reactive nitrogen species and use an alternative electron donor such as the reduced form of nicotinamide adenine dinucleotide. Metronidazole, the current standard of therapy for amebiasis, seems to exert its antiparasitic effect through the inhibition of this antioxidant system. Newer therapeutic candidates targeting this system, such as auranofin, also have demonstrated in vitro and in vivo efficacy against this parasite.

Liver abscesses are always preceded by intestinal colonization, which may be asymptomatic. Blood vessels may be compromised early by wall lysis and thrombus formation. Trophozoites invade veins to reach the liver through the portal venous system. *E. histolytica* is resistant to complement-mediated lysis—a property critical to survival in the bloodstream. In contrast, *E. dispar* is rapidly lysed by complement and is thus restricted to the bowel lumen. Inoculation of amebas into the portal system of hamsters results in an acute cellular infiltrate consisting predominantly of neutrophils. Later, the neutrophils are lysed by contact with amebas, and the release of neutrophil toxins may contribute to necrosis of hepatocytes. The liver parenchyma is replaced by necrotic material that is surrounded by a thin rim of congested liver tissue. The necrotic contents of a liver abscess are classically described as "anchovy paste," although the fluid is variable in color and is composed of bacteriologically sterile granular debris with few or no cells. Amebas, if seen, tend to be found near the capsule of the abscess.

Host innate and adaptive immunity are important factors that determine susceptibility to invasive disease and its clinical outcome. While neutrophils were thought to contribute to tissue damage in intestinal and liver amebiasis due to their cytotoxic effects on host epithelial cells, a recent report suggests that they may exert a protective effect in susceptible mice. Neutropenia, induced with an antibody to Gr-1 (i.e., to peripheral neutrophils), led to death in C3H/HeJ mice and to severe disease in CBA mice (both of which are relatively susceptible to *E. histolytica* infection), while it had no effect on C57BL/6 mice, which are known for their intrinsic resistance to infection with this parasite.

Antimicrobial peptides, such as cathelicidins, are an important part of innate immunity and are induced by *E. histolytica* upon intestinal invasion in a mouse model. In this model, cecal cathelicidin-related antimicrobial peptide (CRAMP) mRNA increased more than fourfold by 3 days and more than 100-fold at 7 days. However, *E. histolytica* remained resistant to cathelicidin-mediated killing, probably because the antimicrobial peptide was digested by amebic cysteine proteinases.

IgA plays a critical role in acquired immunity to *E. histolytica*. A study in Bangladeshi schoolchildren revealed that an intestinal IgA response to Gal/GalNAc reduced the risk of new *E. histolytica* infection by 64%. Serum IgG antibody is not protective; titers correlate with the duration of illness rather than with the severity of disease. Indeed, Bangladeshi children with a serum IgG response were more likely than those without such a response to develop new *E. histolytica* infection. In infants from this same Bangladeshi community, passive immunity conferred by maternal parasite-specific IgA via breastfeeding resulted in a 39% reduction in risk of infection and a 64% reduction in risk of diarrheal disease from *E. histolytica* during the first year of life.

A link between nutrition and immunity is demonstrated by the elevated rate of infections due to protozoan parasites, including *E. histolytica*, among undernourished children in developing countries. Resistance to amebiasis is associated with a polymorphism in the receptor for the adipocytokine leptin. Children in a Bangladeshi cohort with a mutant R223 leptin receptor allele were nearly four times more likely to be infected with *E. histolytica* than those carrying the ancestral Q223 allele. This mutant allele is overrepresented in many geographic areas with a high prevalence of amebiasis, such as Bangladesh and India.

CLINICAL SYNDROMES

Intestinal Amebiasis The most common type of amebic infection is asymptomatic cyst passage. Even in highly endemic areas, most patients harbor *E. dispar*.

Symptomatic amebic colitis develops 2–6 weeks after the ingestion of infectious *E. histolytica* cysts. A gradual onset of lower abdominal pain and mild diarrhea is followed by malaise, weight loss, and diffuse lower abdominal or back pain. Cecal involvement may mimic acute appendicitis. Patients with full-blown dysentery may pass 10–12 stools per day. The stools contain little fecal material and consist mainly of blood and mucus. In contrast to those with bacterial diarrhea, fewer than 40% of patients with amebic dysentery are febrile. Virtually all patients have heme-positive stools.

More fulminant intestinal infection, with severe abdominal pain, high fever, and profuse diarrhea, is rare and occurs predominantly in children. Patients may develop toxic megacolon, in which there is severe bowel dilation with intramural air. Patients receiving glucocorticoids are at risk for severe amebiasis. Uncommonly, patients develop a chronic form of amebic colitis, which can be confused with inflammatory bowel disease. The association between severe amebiasis complications and glucocorticoid therapy emphasizes the importance of excluding amebiasis when inflammatory bowel disease is suspected. An occasional patient presents with only an asymptomatic or tender abdominal mass caused by an ameboma, which is easily confused with cancer on barium studies. A positive serologic test or biopsy can prevent unnecessary surgery in this setting. The syndrome of post–amebic colitis—i.e., persistent diarrhea following documented cure of amebic colitis—is controversial; no evidence of recurrent amebic infection can be found, and re-treatment usually has no effect.

Amebic Liver Abscess Extraintestinal infection by *E. histolytica* most often involves the liver. Of travelers who develop an amebic liver abscess after leaving an endemic area, 95% do so within 5 months. Young patients with an amebic liver abscess are more likely than older patients to present in the acute phase with prominent symptoms of <10 days' duration. Most patients are febrile and have right-upper-quadrant pain, which may be dull or pleuritic in nature and may radiate to the shoulder. Point tenderness over the liver and right-sided pleural effusion are common. Jaundice is rare. Although the initial site of infection is the colon, fewer than one-third of patients with an amebic abscess have active diarrhea. Older patients from endemic areas are more likely to have a subacute course lasting 6 months, with weight loss and hepatomegaly. About one-third of patients with chronic presentations are febrile. Thus, the clinical diagnosis of an amebic liver abscess may be difficult to establish because the symptoms and signs are often nonspecific. Since 10–15% of patients present only with fever, amebic liver abscess must be considered in the differential diagnosis of fever of unknown origin (Chap. 26).

Complications of Amebic Liver Abscess Pleuropulmonary involvement, which is reported in 20–30% of patients, is the most frequent complication of amebic liver abscess. Manifestations include sterile effusions, contiguous spread from the liver, and rupture into the pleural space. Sterile effusions and contiguous spread usually resolve with medical therapy, but frank rupture into the pleural space requires drainage. A hepatobronchial fistula may cause cough productive of large amounts of necrotic material that may contain amebas. This dramatic complication carries a good prognosis. Abscesses that rupture into the peritoneum may present as an indolent leak or an acute abdomen and require both percutaneous catheter drainage and medical therapy. Rupture into the pericardium, usually from abscesses of the left lobe of the liver, carries the gravest prognosis; it can occur during medical therapy and requires surgical drainage.

Other Extraintestinal Sites The genitourinary tract may become involved by direct extension of amebiasis from the colon or by hematogenous spread of the infection. Painful genital ulcers, characterized by a punched-out appearance and profuse discharge, may develop secondary to extension from either the intestine or the liver. Both of these conditions respond well to medical therapy. Cerebral involvement has been reported in fewer than 0.1% of patients in large clinical series. Symptoms and prognosis depend on the size and location of the lesion.

DIAGNOSTIC TESTS

Laboratory Diagnosis Stool examinations, serologic tests, and noninvasive imaging of the liver are the most important procedures in the diagnosis of amebiasis. Fecal findings suggestive of amebic colitis