By Edward Markell, MD, PhD

Amebiasis—or Disparosis?

Until recently,* Entamoeba histolytica *was regarded as a single species. Most practicing physicians are still unaware that E. histolytica often does not cause symptoms in individual patients but always has pathogenic potential and may cause asymptomatic infection, whereas the much more common Entamoeba species,* Entamoeba dispar*, is always nonpathogenic and should not be treated. Unfortunately, most laboratories are likewise unaware of these facts and cannot differentiate between the two species; the organism should therefore be reported by these laboratories as* E. histolytica/dispar *complex. Practical methods for accurate diagnosis are discussed; when these methods are used by clinical laboratories, physicians will be able to treat selectively those patients who are infected with the potentially pathogenic species. Treatment of amebiasis is not discussed.

Introduction

When diagnosing a patient who has a medical history and clinical findings suggestive of infectious enteritis, physicians usually start their investigation by ordering a stool culture and one or more stool specimens to be examined for protozoa and other parasites. If the initial culture result is negative and the laboratory identifies *Entamoeba histolytica*, treatment for that parasite will probably be given, and subsequent investigation will be curtailed. However, recent discoveries suggest that this approach may be incorrect most of the time, because we now know that what has been considered *E. histolytica* actually includes two distinct species, the much more common of which is always nonpathogenic. The purpose of this short account is to alert physicians (and perhaps with their help, laboratories) to the importance of distinguishing between the two species of amebae.

Differences Between Entamoeba Species

Entamoeba histolytica was first described in 1875, after being found in the stools of a dysenteric patient in St. Petersburg, Russia. The pathogenicity of the organism was not fully accepted until some years later, and controversy has remained because amebae morphologically indistinguishable from *E. histolytica* have been found in many asymptomatic patients. In 1925, Brumpt proposed the name *Entamoeba dispar* (dispar = different) for these nonpathogenic amebae. This name was not generally accepted, although it became obvious over the years that there were considerable "strain differences" among amebae having the microscopic characteristics of *E. histolytica*.

More recent work—that of a British researcher[1,2]—also casts doubt on the single-species concept. By performing enzyme electrophoresis on a large number of cultures from different isolates of what were all morphologically determined *E. histolytica*, this researcher identified 20 different electrophoretic patterns, which he named zymodemes. These patterns could be readily reproduced. Eight of these isolates are found consistently in patients with clinical amebiasis (although they are also found in some asymptomatic patients), whereas 12 isolates derive from strains known to always produce asymptomatic infections. Good correlation was subsequently shown between the zymodeme status of a particular isolate and the presence or absence of a serologic antibody response in the patient: >90% of patients infected with a pathogenic zymodeme had this antibody response, which was seen in <5% of patients with nonpathogenic zymodemes.

Still more recent research analyzing molecular differences between pathogenic and nonpathogenic amebae gives ample evidence for their genetic specificity—a fact not widely publicized to the medical community. These techniques (not discussed here) are time-consuming and not suitable for the clinical laboratory; however, a simple and quick stool antigen test can now be used to differentiate the two species. The test is readily available but is not used by most laboratories.

It is not clear that we are dealing with two species of amebae with the same microscopic appearance—*E. histolytica* and *E. dispar*. (A third species—*E. hartmanni*—is identical in appearance to the other two species but is easily distinguished because of its smaller size.) Unfortunately, few if any clinical laboratories attempt to distinguish between the two larger species, reporting both as *E. histolytica* and leaving a problem of which clinicians are probably not aware. The nonpathogenic species, *E. dispar*, is generally agreed to be about ten times as common worldwide as the pathogenic species, *E. histolytica*.

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Clinical Recommendations

How should physicians respond to a laboratory diagnosis of amebiasis? First, they need to know whether the laboratory reporting *E. histolytica* has identified the pathogenic organism—an event which seldom occurs at present. Perhaps at the urging of physicians, more and more laboratories will recognize the importance of distinguishing between the two species. If a laboratory does not yet differentiate pathogenic from nonpathogenic species, then any reported *E. histolytica* should be treated, even in asymptomatic patients, because symptoms may appear in that person later and because the patient may carry infection to others. In this regard, clinical judgment should be modified by the realization that the pathogen is considerably rarer than previously believed.

How should clinical laboratories resolve this problem? First, they must stop the practice of automatically reporting as *E. histolytica* all amebae which look like that organism. Instead, the finding should be reported as *E. histolytica/dispar* complex if no further clues to the true identity of the parasite are found. This solution presupposes that both the physician and the laboratory technician are aware of *E. dispar*, which unfortunately is not yet the case. Nonetheless, the true pathogen may be distinguished on the prepared slide: If trophozoites containing red blood cells are seen in the preparation, the species is surely *E. histolytica*, and no further studies are needed; if the amebae lack red blood cells, their presence in a stool specimen containing such amebae provides strong presumptive evidence of pathogenicity, which can then be confirmed by identification of the specific *E. histolytica* stool antigen or by testing blood for specific antibodies (which are not evoked by *E. dispar*).

A number of tests exist for amebic antigens in stool, and almost all purport to diagnose *E. histolytica*; however, these tests may actually react to antigens present in both amebae and so are diagnostic only of the *E. histolytica/dispar* complex. This limitation is true not only of tests available to the clinical laboratory in kit form but also of tests performed by commercial and governmental laboratories. One monoclonal antibody test has been designed to react to an adherence lectin produced by *E. histolytica* (and not by *E. dispar*) and thus can be used with high specificity to identify the former organism.[3] The test is commercially available in kit form from TechLab, 1861 Pratt Drive, Blacksburg, Virginia 24060-6364 (telephone 1-800-TECHLAB). One major disadvantage of this test is that it must be done on fresh (unpreserved) stool specimens. At present, one Kaiser Foundation Health Plan (KFHP) clinical laboratory is collaborating with the maker of the monoclonal antibody test to determine whether preserved stools can be used in such testing; results of this collaborative study are not yet available.

Although this monoclonal antibody test is reliable, the relative rarity of amebiasis in the general population suggests that the test should not be used for random screening but should instead be reserved to differentiate between the two amebae species when the laboratory cannot otherwise do so. The *E. histolytica/dispar* complex is believed to be present in only 3% of the general US population, suggesting that true amebiasis may be found in only one tenth that number of people. (Ravdin[4]) published an excellent, detailed article about the epidemiology, pathogenesis, clinical presentation, diagnosis, and treatment of intestinal amebiasis as well as its extraintestinal complications. Of course, prevalence of this condition varies considerably from group to group. Much higher rates of exposure than in the US may be found among travelers (especially if they reside for any length of time in third-world countries, where *E. histolytica* may be both more prevalent than in the US and more common than *E. dispar*), among immigrants from such countries, and among those who closely associate with these immigrants. Even in a single geographic area, prevalence may vary greatly from group to group. For example, on the basis of two stool examinations each, an organism which had initially been described as *E. histolytica* (but which probably included both amebae of the *E. histolytica/dispar* complex) was found in the stools of only 0.72% (99% confidence level 0.1-2.6%) of a fairly representative group of 415 KFHP members in the San Francisco Bay Area, selected on the basis of having tests done as part of a routine physician examination.[5] These patients were found not to have statistically significantly different or more frequent gastrointestinal complaints than members preparing for the same type of examination who were not asked to participate in the stool check. On the other hand, what was then identified as *E. histolytica* was found in the stools of 28.6% of 508 homosexual men in the same geographic area.[6] Other research has given similar results, although no published reports have as yet differentiated *E. histolytica* from *E. dispar*.

Conclusion

At present, the stool antigen test specific for *E. histolytica* is not yet available, but clinicians and laboratories should be alert to the importance of distinguishing between *E. histolytica* and *E. dispar*. Labo-

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ratories unable to distinguish these species should report them as *E. histolytica/dispar* complex, and clinicians would be well advised to treat all cases of *E. histolytica* infection until an accurate diagnostic test becomes readily available for differentiating between the two species. ❖

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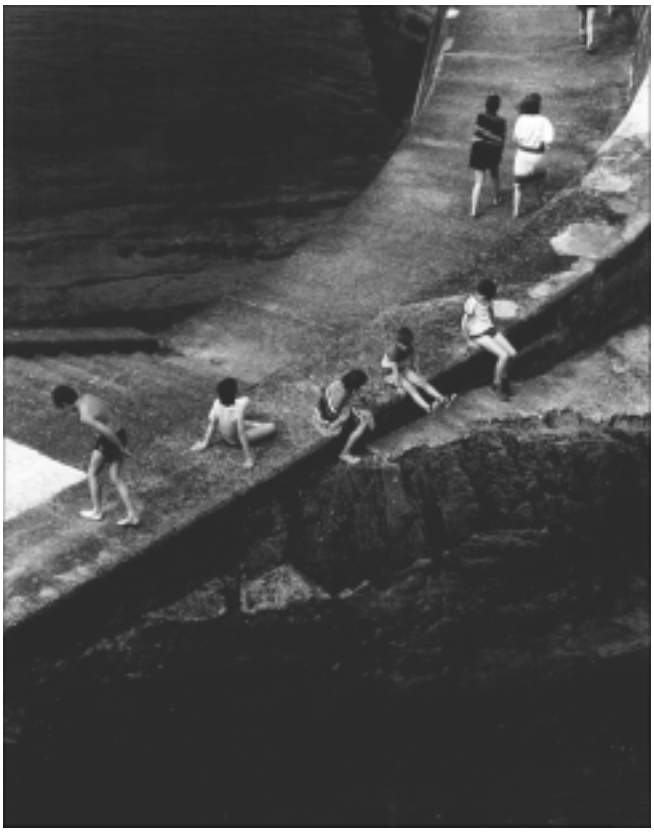

"Pier, Ardmore" by Eric Blau, MD.
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