LEISHMANIASIS

Introduction

Leishmaniasis refers to a collection of clinical manifestations that are the result of a protozoal infection by members of the *Leishmania* family. Leishmaniasis generally does not spread from person to person; rather, infections are transmitted to people when they are bitten by an infected female sandfly. It is important to be aware of this infection because some of the symptoms found in infected patients are similar to those reported by some Gulf War veterans. Furthermore, a small number of Gulf War veterans have already been diagnosed as having leishmaniasis. Understanding what is known about infections with this organism, including the diseases it produces, can help put this infection in the overall context of the Gulf War illnesses. Although not all forms of leishmaniasis are known to exist in the Persian Gulf, this section begins with a discussion of leishmaniasis in general and then focuses on specific infections known to occur in the Middle East.

*Leishmania* is a microscopic parasite that can be seen only by trained professionals using a relatively high-powered microscope. The life cycle of the organism is interesting although not unique in nature. *Leishmania* are digenetic protozoa, meaning that they exist in two distinct life forms. *Leishmania* live in specific animal hosts (sometimes including humans) as aflagellar obligate intracellular amastigotes (2–3 µm in length) within mononuclear phagocytes. The organisms are transmitted from animal to animal (or animal to human) through an insect intermediate, particularly the sandfly, *Phlebotomus papatasi*, where *Leishmania* exist as flagellated, extracellular promastigotes (10–15 µm in length and 1.5–3.5 µm in width). To acquire the infection, the sandfly must first bite an infected animal (or person). Then the *Leishmania* organism transforms itself from the amastigote to the promastigote form in the sandfly. The infection is
passed when the infected sandfly feeds on a new victim. From the standpoint of human disease, the usual animal host serves as the reservoir.

Different *Leishmania* species have traditionally been thought to cause different diseases, although they look the same when viewed under the microscope. The different species have been distinguished by the way they clinically affect their victims (hosts) and their geographic origin. Experts have recognized and classified the infections into four distinct clinical syndromes: cutaneous leishmaniasis, visceral leishmaniasis (known also as kala azar), mucocutaneous leishmaniasis, and diffuse cutaneous leishmaniasis. The first two are of interest to Gulf War veterans because the infectious organisms that cause these diseases exist in the Persian Gulf region.

Tables 6.1 and 6.2 show the common associations between cutaneous and visceral *Leishmania* infections, respectively, and the organisms that cause them.

### Epidemiologic Information

Leishmaniasis is of interest in studying Gulf War illnesses because it is known to exist in the Persian Gulf region, because it causes a number of different symptoms, some of which are included in the Gulf War illnesses, and because leishmaniasis has been found in some Gulf War veterans. By early 1995, there were 12 cases of viscerotropic and 20 cases of cutaneous leishmaniasis diagnosed in U.S. troops who served in the Gulf War (Hyams et al., 1995). Cutaneous

### Table 6.1

**Old World Cutaneous Leishmaniasis**

<table>
<thead>
<tr>
<th>Organism</th>
<th>Geographic Areas</th>
<th>Animals Infected</th>
<th>Age/Gender Distribution</th>
<th>Incubation Period</th>
<th>Symptoms</th>
<th>Resolution</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Leishmania</em></td>
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<tr>
<td><em>tropica</em></td>
<td>Mediterranean Desert</td>
<td>Humans and dogs</td>
<td>Urban children and younger adults</td>
<td>2–24 months</td>
<td>Single sore, usually on the face, slowly enlarges, crusty appearance</td>
<td>Heals over 1–2 years and scars, rarely spreads</td>
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<tr>
<td></td>
<td>India</td>
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<td></td>
<td>Southern</td>
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<tr>
<td></td>
<td>Soviet Union</td>
<td></td>
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<td></td>
</tr>
<tr>
<td><em>Leishmania</em></td>
<td></td>
<td>Burrowing rodents and humans</td>
<td>All rural populations</td>
<td>2–8 weeks</td>
<td>Multiple sores, usually on legs, sometimes swollen lymph glands, moist appearance</td>
<td>Heals in 3–5 months with scarring</td>
</tr>
<tr>
<td><em>major</em></td>
<td>Middle East Deserts</td>
<td></td>
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<tr>
<td></td>
<td>Africa,</td>
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<td></td>
<td>Southern</td>
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<tr>
<td></td>
<td>Soviet Union</td>
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</tr>
</tbody>
</table>


NOTE: The cutaneous leishmaniasis types shown are the major ones associated with “old world cutaneous leishmaniasis.” There are a number of “new world” types, but, since they are not likely to be relevant to those with Gulf War illnesses, they have not been included in this chart.
Table 6.2
Visceral Leishmaniasis

<table>
<thead>
<tr>
<th>Organism Subtype</th>
<th>Geographic Areas</th>
<th>Animals Infected</th>
<th>Age Distribution</th>
<th>Incubation Period</th>
<th>Symptoms</th>
<th>Resolution</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Leishmania donovani</em></td>
<td>African East Africa mostly</td>
<td>Dogs, other meat eating animals, humans</td>
<td>Ages 10–25</td>
<td>3 months (range 1–18 months)</td>
<td>Nighttime fevers, rapid heart rate, diarrhea, cough, liver problems, sometimes swollen lymph glands, anemia, and other blood problems</td>
<td>Requires treatment</td>
</tr>
<tr>
<td>Mediterranean (a.k.a. <em>L. infantum</em>)</td>
<td>Mediterranean, China, Soviet countries</td>
<td>Dogs, jackals, foxes, humans, and probably rats</td>
<td>Infants usually; sometimes adults</td>
<td>Same as above</td>
<td>Same as above</td>
<td>Requires treatment</td>
</tr>
<tr>
<td>Mediterranean (a.k.a. <em>L. chagasi</em>)</td>
<td>Latin America</td>
<td>Dogs, jackals, foxes, and humans</td>
<td>Infants usually; sometimes adults</td>
<td>Same as above</td>
<td>Same as above</td>
<td>Requires treatment</td>
</tr>
<tr>
<td>Indian</td>
<td>India</td>
<td>Humans only</td>
<td>Ages 10–25</td>
<td>Same as above</td>
<td>Same as above</td>
<td>Requires treatment</td>
</tr>
</tbody>
</table>


Leishmaniasis was a known infectious disease problem for troops stationed in the Middle East during World War II, with an incidence of 1.93 cases per 1,000 population (“Unexplained illnesses among Desert Storm veterans . . . ,” 1995; Cross and Hyams, 1996); therefore, it was anticipated that it might become a problem during the Gulf War. However, the incidence of leishmaniasis among Gulf War ground troops was only about 2–3 percent of that experienced in World War II.

What Infected Patients Experience

The specific symptoms experienced by infected individuals depend on the type of infection. Cutaneous and visceral disease are discussed separately.

Cutaneous Leishmaniasis. After infection, patients usually present with findings after two to eight weeks (the incubation period), although some cases have been reported following a one-year incubation period. The first is usually a reddish, inflamed swelling or lump that begins at the site of the sandfly bite. Over the next few months, the swelling grows until ultimately the skin opens in the form of an ulcer with a raised border and a crusty center. Because the sandfly generally bites its victim on exposed areas of the skin (e.g., face, extremities), these are the sites of most nodules and ulcers.
Classically, the organisms known to cause cutaneous leishmaniasis in the Middle East are *Leishmania tropica* and *Leishmania major*. Twenty cases of cutaneous leishmaniasis were diagnosed among Gulf War troops (Kreutzer et al., 1993). Among Gulf War troops, *L. major* was the cause of the cases of cutaneous leishmaniasis.

**Visceral Leishmaniasis.** Visceral leishmaniasis refers to the disseminated form of the disease; that is, patients with visceral leishmaniasis have an infection that involves multiple organs in the body. In its full-blown form, visceral leishmaniasis, known as kala azar, is a devastating disease with a high mortality rate. Visceral disease is classically associated with an infecting organism known as *Leishmania donovani*. Gulf War veterans, however, experienced the visceral form of the disease as a result of infection with *L. tropica*, a different species of *Leishmania* that is generally associated with the cutaneous form of the disease.

Most important, the visceral disease experienced by Gulf War troops appears to have been of a milder visceral form than that conventionally known. The disease is sufficiently different that it has been termed “viscerotropic” (meaning having an attraction to the body organs) leishmaniasis to distinguish it from classical visceral disease (Magill et al., 1993).

Magill described the findings found in the first eight patients; these are summarized in Table 6.3.

Two of these eight patients had other serious diseases; one was infected with HIV and another had a serious cancer of the kidney. The remaining six patients were otherwise healthy.

<table>
<thead>
<tr>
<th>Feature</th>
<th>Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incubation period</td>
<td>1–14 months</td>
</tr>
<tr>
<td>Fever</td>
<td>5 of 8 patients</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>6 of 8 patients</td>
</tr>
<tr>
<td>Tiredness</td>
<td>7 of 8 patients</td>
</tr>
<tr>
<td>Fatigue</td>
<td>7 of 8 patients</td>
</tr>
<tr>
<td>Enlarged liver</td>
<td>4 of 8 patients</td>
</tr>
<tr>
<td>Enlarged spleen</td>
<td>4 of 8 patients</td>
</tr>
</tbody>
</table>

**Diagnosis**

Cutaneous leishmaniasis can be diagnosed histologically. The organisms appear in biopsy sections as round to oval bodies measuring from 2 to 4 µm without a capsule. The organisms are found within macrophages, sometimes up to
20 organisms within a single macrophage (Lever and Schaumburg-Lever, 1983). Culture is also an available diagnostic method that permits speciation of the parasite.

Diagnostic procedures for visceral leishmaniasis are considerably more invasive than those described for the cutaneous form. Because the organism resides in tissues, bone marrow aspirate and biopsy, lymph node biopsy, liver biopsy, and splenic biopsy are diagnostic options used in various countries (Locksley, 1991). Staining techniques similar to those described for the cutaneous form of the disease are then used to identify the organism. Current serologic assays (tests to look for evidence of infection using blood samples) are neither sensitive nor specific. Although new assays continue to be developed (Dillon et al., 1995), much additional research in this area is warranted to be able to better detect and understand the distribution of diseases caused by *Leishmania*.

**Treatment and Prevention**

Pentavalent antimonial compounds for three to four weeks are the first-line treatment drugs for patients with visceral leishmaniasis and for patients with the cutaneous form of disease when lesions are disfiguring or where mucocutaneous disease is prevalent. For patients with cutaneous disease that is not disfiguring, it is reasonable either to observe the patient or to treat with topical agents.

Most patients with visceral disease respond to treatment, although the rate of resistance to initial therapy, currently about 10 percent, is increasing. It is important, therefore, to ensure an accurate diagnosis before treatment and follow treatment guidelines explicitly.

Prevention centers on avoidance of sandfly bites. Spread can be prevented by using insecticides and mosquito nets to protect the infected individual from sustaining another bite, permitting subsequent transmission to an uninfected host. Further information can be found in the review of *Leishmania* by Oldfield and colleagues (1991).

**Correlation with Gulf War Illnesses**

Although it is possible that additional Gulf War veterans may have had viscerotropic leishmaniasis, the infection is unlikely to be present in a large population of Gulf War veterans. First, all patients who were identified with the disease were identified within just over a year following exposure. Second, the cutaneous disease, unlike the viscerotropic form, is easy to see and it is unlikely
that more individuals would not have sought treatment if there was a major outbreak.

*Leishmania* is transmitted by the same vector, *Phlebotomus papatasi*, that causes sandfly fever. There were no cases of sandfly fever reported among Gulf War veterans, in contrast to the 30 cases of sandfly fever per 1,000 population (among those deployed to the Middle East) during World War II. The time of year when most troops were deployed during the Gulf War favored the low rate of *Leishmania* infection and the absence of sandfly fever. *Leishmania* must go through the promastigote stage in the sandfly, and a significant sandfly population exists in the region only during certain seasons. The prevalence of *P. papatasi* depends on environmental conditions; the sandfly is sensitive to temperature extremes and low humidity.

Cross and colleagues (1996) used weather station and satellite data to model Persian Gulf weather conditions and predict the seasonal distribution of the sandfly. Figure 6.1 shows the approximate results of the model and indicates that the highest sandfly prevalence, and thus the highest risk of both *Leishmania* and sandfly fever, occurs in the spring and summer months.

Because the sandfly is responsible for both the cutaneous and the viscerotropical form, a low rate of cutaneous disease suggests similar results for the more invasive form. Of the 12 patients identified with viscerotropic disease, only one was asymptomatic. Therefore, if the viscerotropic disease were more common, more patients with severe abdominal pain, fever, abnormal laboratory tests, and fatigue would be expected.

Similarly, although there is little experience with visceral disease caused by *L. tropica*, several of the patients studied extensively and reported by Magill et al. (1993) were not treated, and yet their disease resolved. This duration of illness and resolution is unlike that seen in kala azar, but it is similar to how the *L. tropica* organism behaves when it causes cutaneous disease.

There is no known evidence that *Leishmania* per se interacts with other infectious diseases or agents. Like any other infectious agent, however, *Leishmania*

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1 Leishmaniavirus, recognized relatively recently (1988), is a double-stranded RNA virus that infects some strains of *Leishmania* (Chung et al., 1994). This virus is a member of the family Totiviridae, a group of viruses that infect protozoa and fungi (Saiz et al., 1998). Leishmaniavirus has some unusual characteristics; specifically, a viral capsid protein is an RNA endonuclease that may be responsible for some of the viral persistence characteristics (MacBeth and Patterson, 1995). The virus has been detected in cultured *L. braziliensis*, *L. b guyanensis*, and *L. major* (Saiz et al., 1998). Further research is needed to sufficiently understand the role of this virus in the pathogenesis of human disease. There is some speculation that the virus might modify the protozoan infection and influence the manifestations of disease in patients infected with *Leishmania*. At present, however, there is no evidence that sufficient patients are infected with *Leishmania* that Leishmaniavirus could be present in more than, at most, a few individuals who served in the Gulf War.
interacts with the host’s immune system. In fact, this interaction is responsible for much of the damage that occurs as a result of the infection. Some evidence suggests that a suppressed immune system, as occurs with AIDS and other diseases, can result in leishmaniasis taking on different manifestations. Immune system responses are covered in companion reports in this series, including the volume on stress (Marshall et al., 1999).

Review of the findings, particularly viscerotropic leishmaniasis, suggests that patients with leishmaniasis share some clinical symptoms (e.g., fatigue) with some patients with undiagnosed illnesses associated with Gulf War service. There has been considerable interest in those few Gulf War veterans known to be infected with this parasite.
Summary

*Leishmania* is important because infection is known to exist in the Middle East, military personnel and veterans are known to have become infected, and the symptoms resemble those of Gulf War illnesses. Presently, simple diagnostic tests for visceral and viscerotropic disease do not exist, although research to develop these tests is under way and should be accelerated. The finding of 12 cases of viscerotropic leishmaniasis caused by *L. tropica* reminds us that all the possible manifestations of infectious diseases are not known.

Leishmaniasis was a known infectious disease at the onset of Operation Desert Shield. Efforts to prevent exposure to the sandfly likely helped reduce the number of patients who ultimately became infected with the disease. Also, the timing of the operation was favorable in that the sandfly population increases during spring and summer months. Many military and civilian documents suggest a high level of understanding of where *Leishmania* exists and what steps can be taken to prevent or reduce it when U.S. troops are stationed in areas where it lives.

Because all of the known cases of leishmaniasis were diagnosed within just over a year after the Gulf War, it is unlikely that *Leishmania* is a major cause of unexplained Gulf War illnesses.

MALARIA

Introduction

Malaria in humans is caused by one of four plasmodia species that infect humans: *P. falciparum*, *P. vivax*, *P. ovale*, and *P. malariae*. Malaria has been recognized for over 3,500 years and is found primarily in Africa, Asia, South and Central America, and Oceania regions.

Seven cases of *P. vivax* were observed among individuals who served in the Gulf War. Malaria remains a serious problem, particularly in developing countries, with over 200 million cases and between one million and two million deaths annually. Malaria is also recognized as a particular problem for both military and civilian individuals who travel to areas where malaria is endemic.

Malaria is usually transmitted to humans through the bite of the infected female anopheline mosquito. Once they enter the body, the four species interact with the host somewhat differently. With all four, the sporozoite form present in mosquito saliva travels through the body to the liver. In the liver, they invade the liver cells (hepatocytes) and mature to become tissue schizonts (all four forms) or dormant hypnozoites (seen in *P. vivax* and *P. ovale*).
The schizonts produce thousands of merozoites (an amplification stage) after which they rupture the liver cell and are released into circulation to invade red blood cells. Within the red cells, the merozoites multiply, producing 24–32 offspring that, upon lysis of the red cell, continue the cycle by infecting subsequent erythrocytes. For *P. vivax* or *P. ovale*-infected individuals, hypnozoites can remain dormant for a number of months before they mature into schizonts, releasing merozoites into the blood and causing either a relapse or a delayed initial infection (most likely to occur in individuals taking prophylactic drugs during travel to endemic areas).

Within erythrocytes, some organisms develop into a gametocyte form (the sexual stage). The gametocytes enter the mosquito at the time of an insect bite, mature into gametes and then divide to produce the sporozoites. Sporozoites migrate to the mosquito salivary gland and then enter a new host upon a subsequent bite.

Patients may become infected through blood transfusion or through transmission during pregnancy. In these cases, there is not a relapsing course associated with *P. vivax* or *P. ovale* because no hypnozoite stage is established through initial hepatic infection.

**Epidemiologic Information**

*P. falciparum* occurs primarily in tropical areas throughout the world whereas *P. vivax* is common in tropical and temperate areas, *P. malariae* occurs worldwide, and *P. ovale* is less common with most cases identified in Western Africa, India, and South America. It is not surprising, therefore, that the seven patients with malaria were diagnosed with *P. vivax* infections. In more temperate areas where mosquitoes are prevalent only during summer months, the hypnozoite stage of *P. vivax* allows parasite survival in humans over the winter so that the infection can be again transmitted when the mosquito population increases in summer.

Among civilians in the United States (including foreigners and those of unknown origin), there were 151 cases of malaria in 1970, increasing to 1,838 in 1980 and dropping back to 976 in 1994 (Centers for Disease Control, 1997b).

**What Infected Patients Experience**

Fever cycles are the hallmark of malarial infection. Erythrocyte lysis with release of merozoites occurs usually just after a fever spike. The cycle frequency provides some insight into the type of malaria present. With *P. vivax* and *P. ovale*, cycles occur approximately every 48 hours whereas with *P. malariae* the
cycle is 72 hours. Patients with *P. falciparum* infections usually experience ongoing fevers with intermittent fever spikes. The cycle is characterized by a prodromal stage of several hours followed by a cold stage that can last minutes to hours and is often accompanied by shaking chills. Then the patient experiences the hot stage with a rapid fever rise around the time of schizont rupture. During these high fevers (up to or greater than 104°F), headache, hypotension, tachycardia, nausea, vomiting, diarrhea, and altered mental status are common. Several hours later the patient, who during the hot stage was relatively dry, enters a diaphoretic stage with profound sweating, defervescence, and fatigue.

By far the most dangerous form of malaria is the illness caused by *P. falciparum*. Only *P. falciparum* produces microvascular disease that results from adherence of the infected cells to endothelial cells of capillaries and small veins. This adherence blocks these vessels. Combined with other pathophysiologic effects, *P. falciparum* precipitates damage to essential organs, particularly the brain (cerebral malaria), kidney (renal failure), gastrointestinal tract (gastroenteritis), and lungs (pulmonary edema).

The other forms of malaria do not produce the microvascular disease observed with *P. falciparum*. *P. vivax* and *P. ovale* tend to infect younger erythroid cells (reticulocytes), therefore limiting the erythrocyte population they target. However, as they lyse reticulocytes, these parasites stimulate increased red cell hematopoiesis, increasing the number of younger erythroid cells in the peripheral blood.

**Diagnosis**

From the clinical standpoint, malaria should be included in the differential diagnosis when a patient presents with fever in the presence of any risk factor for transmission, particularly travel to endemic areas. Diagnosis is established by finding parasites in Giemsa-stained blood films obtained from infected individuals. It may be necessary to draw several specimens to properly identify the organism. Although some sensitive blood tests are available through the CDC, they are not routinely available in diagnostic laboratories, nor are they necessary to establish the diagnosis.

**Treatment and Prevention**

Treatment for malaria is well established, with chloroquine being the drug of choice for infections that are susceptible to this drug. Almost all cases of *P. vivax* are susceptible, although drug resistance can present a challenge to physicians treating patients infected with *P. falciparum*. Patients with resistant *P.
vivax respond to other medications to eradicate the initial infection. Individuals infected with P. vivax and P. ovale are also treated with primaquine to obliterate the hypnozoites, preventing a relapse months after initial symptoms resolve (“Mefloquine and malaria prophylaxis,” 1998; McCombie, 1996; Olliaro et al., 1996; White, 1997, 1998; Barat and Bloland, 1997).

A number of preventative strategies exist or are the subject of research. Current strategies include chemoprophylaxis for individuals traveling to endemic areas, vector control (mosquito abatement programs and insecticides), and use of repellants and mechanical barriers to mosquitoes. Vaccination is the subject of current research (Barron, 1998; Mills, 1998; Kain and Keystone, 1998; Kwiatkowski and Marsh, 1997; Kitua, 1997; Soares and Rodrigues, 1998; Connor et al., 1998; Greenwood, 1997; Facer and Tanner, 1997; Dubois and Pereira da Silva, 1995; Leo et al., 1994).

**Correlation with Gulf War Illnesses**

Because of the public health effect of malaria, infections with this organism are quite well understood. Regarding patients who returned to the United States with malaria, fewer than 5 percent of them became ill more than one year after arriving in the United States.

The known behavior of the *Plasmodium* species indicates that malaria is an extremely unlikely etiology for unexplained Gulf War illnesses. All seven individuals who served in the Gulf War with malaria were diagnosed with *P. vivax.* Judging by clinical experience, very few patients initially present after one year. The constellation of symptoms included among those with unexplained Gulf War illnesses is inconsistent with what we know about malaria.

**Summary**

Malaria is known to exist in the Middle East, and a few military personnel and veterans were infected, experiencing classic malaria symptoms. Experienced laboratories should have no difficulty identifying the malaria parasite on commonly used blood films, yet blood work on individuals with unexplained Gulf War illnesses has been repeatedly negative.

The clinical presentation of unexplained Gulf War illnesses is inconsistent with what we know about the clinical course of malaria. Almost all malaria cases manifest disease within the first year following exposure. The likelihood of persistent, subclinical disease is very remote.
GIARDIA

Introduction

Giardiasis is an illness caused by *Giardia lamblia* (also called *G. intestinalis* or *G. duodenalis*), a one-celled, microscopic parasite that lives in the intestines of people and animals. This parasite belongs to the family *Hexamitidae*. The organism is a flagellated enteric protozoa that is a common cause of morbidity throughout the world, including the United States. Primary findings in infected patients include diarrhea, abdominal cramps, bloating, and gas. Some estimate that *Giardia* accounts for up to 25 percent of North American gastroenteritis.

*Giardia lamblia* is a teardrop-shaped multiflagellar parasite that infects the upper small bowel of humans and other animals. This form of the organism is too fragile to survive outside the gut, but with normal bowel activity, *Giardia* transform and protect themselves in a membrane and undergo division to form cysts with four nuclei (Lujan et al., 1997). It is these cysts that are infective through the fecal-oral route. Cysts can survive in water for several months. Ingestion of 10 cysts can result in disease (Ortega and Adam, 1997). When in the gut, the parasite impairs absorption, particularly of fats and carbohydrates (Plorde, 1991b). As the organism populates the small intestine, it produces the clinical manifestations associated with giardiasis.

Epidemiologic Information

*Giardia* is ubiquitous. Random evaluation of stool suggests that there is a prevalence of about 4 percent in the United States (Hill, 1995). In other countries, the prevalence may exceed 20 percent (Plorde, 1991b). The most frequent source of infection is ingestion of contaminated water; drinking or swimming in unfiltered surface fresh water constitutes a potential risk as does travel to foreign countries with impure water and food supplies. Person-to-person transmission is the second most common source of infection, particularly for children in day care centers (especially if diapering is done), those caring for children in these centers, homosexual males, and institutionalized individuals (Hill, 1995; Thompson, 1994).

What Infected Patients Experience

The incubation period is typically one week, and the disease generally lasts 1–2 weeks, although a much longer duration, even years, is possible. The principal symptom is diarrhea (89 percent); other common findings include malaise (84
percent), flatulence (74 percent), foul-smelling greasy stools (72 percent), abdominal cramps (70 percent), bloating (69 percent), nausea (68 percent), anorexia (64 percent), and weight loss (64 percent) (Hill, 1995). Not all patients will be symptomatic; however, asymptomatic patients can still pass infective cysts. Stool examination for cysts at the time of symptom onset may be negative. In some patients, disease may persist for months with significant morbidity related to malabsorption and weight loss. The illness usually resolves after 1–4 weeks, although some patients develop an intermittent chronic infection with flatulence, abdominal pain, and soft stools.

**Diagnosis**

The standard for diagnosis of *Giardia* remains the identification of cysts or trophozoites in fecal material (Plorde, 1991b; Hill, 1995; Cook, 1995). As indicated, during the initial symptomatic phase organisms may not be identifiable in the stool. An alternative is the string test (Enterotest), whereby a nylon string or gastric tube is inserted through the mouth into the duodenum to sample contents. Serologic tests and other sensitive methods are also available to help the physician make the diagnosis of, and research the international distribution of, *Giardia*.

**Treatment and Prevention**

Prevention focuses on decreasing exposure to potentially infected water supplies and exercising caution when handling possibly infected body fluids. Individuals should, consistent with good general hygiene, wash hands after using the bathroom, after handling diapers, and before fixing food or drink. Individuals who are camping or traveling in foreign lands should avoid drinking improperly treated water. Water should be boiled for 10 minutes, chlorinated, or iodinated when uncertainty exists. Generally, municipal water supplies are considered safe. Swimming pools can be a source of infection; therefore, children with diarrhea should not swim.

A number of drugs are available for the treatment of giardiasis (Zaat et al., 1997). The dosing strategies (single dose, multiple doses over several days) vary depending on the drug and the patient population. In addition to specific antimicrobial therapy, supportive care in terms of fluid and electrolyte replacement is important. During treatment, household and sexual contacts should be examined and treated, even if asymptomatic, to prevent reinfection.

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2 CDC website: [http://www.cdc.gov/ncidod/dpd/giardias.htm](http://www.cdc.gov/ncidod/dpd/giardias.htm)
Correlation with Gulf War Illnesses

The clinical findings associated with giardiasis have been discussed. Because *Giardia* is a common infection, it is not surprising that some individuals who served in the Gulf War may have been, or currently are, infected with this parasite. However, the most common finding, namely, self-limited gastrointestinal disease, is not consistent with the long-term manifestations expressed by those individuals with undiagnosed Gulf War illnesses.

Summary

*Giardia* is a parasite that infects individuals either through the consumption of infected water or food or through person-to-person contact. The disease is usually self-limited, over a period of weeks, with the major complaints being gastrointestinal discomfort and diarrhea. Reliable diagnostic tests currently exist to aid in the diagnosis of this disease, the standard being demonstration of the organism in stool or duodenal contents. Although a number of Gulf War veterans are likely to have *Giardia* because it is ubiquitous, the clinical manifestations of this disease are not consistent with most medical complaints expressed by individuals with undiagnosed Gulf War illnesses.

AMOEBA

Introduction

Amebiasis is a disease of the large intestine caused by a one-celled parasite called *Entamoeba histolytica*. This parasite is found in the United States and around the world. In most infected individuals, the disease is asymptomatic, although there is a spectrum of presentation, ranging from mild diarrhea to life-threatening dysentery. A number of species of amoeba naturally parasitize humans, but it is *E. histolytica* that is important in disease. Some individuals, particularly those who are immunosuppressed (e.g., on steroids, HIV infected, suffering from malnutrition), are at high risk of developing serious disease.

*E. histolytica* is a protozoa that is within the family *Entamoebidae*. The organism has a fairly simple life cycle. It exists in two forms—the mobile trophozoite and the cyst form. The trophozoite form is the one responsible for disease and lives either within the colon or in the wall of the colon (responsible for disease), living on bacteria and other material within the gut. When diarrhea occurs, the trophozoite can be seen in liquid stool by trained observers. Under usual circumstances, however, the organism usually encysts before it leaves the GI tract. The cysts can survive for weeks in moist environments whereas trophozoites
die rapidly. The organism is passed from person to person through ingestion of cysts from contaminated water or produce, or via direct fecal-oral spread.

**Epidemiologic Information**

Man is the principal host for amebiasis although the organism can occasionally infect animals. The source of infection is the cyst that enters the stool in asymptomatic patients. Therefore, this infection is most prevalent where living conditions and socioeconomic factors favor its transmission. The disease is most common in impoverished areas, when knowledge of disease transmission is absent, and among individuals who are mentally impaired. The main predisposing factor is poor sanitation resulting in either direct fecal-oral spread or through ingestion of contaminated water or food. There are estimates that half of individuals in developing countries are infected, compared with about a 1–4 percent infection rate in the United States as a whole and a worldwide infection rate of about 10 percent (Plorde, 1991a; Ravdin, 1995). In the United States, the disease is most often seen in immigrants from developing countries, in homosexual men, particularly those who engage in anal-oral sex, and in those living in unclean domiciles.

**What Infected Patients Experience**

For the most part, individuals infected with *E. histolytica* are either asymptomatic or develop only mild intestinal symptoms, including abdominal tenderness or discomfort, loose or watery stools, and stomach cramping. These clinical findings are not unique to *E. histolytica*; other infections cause similar clinical presentations. Even though most strains are not invasive, treatment of all infected individuals is warranted.

Among symptomatic patients, the range of disease extends from intermittent diarrhea to fulminant dysentery. *E. histolytica* has a lytic effect on tissue, the reason for its name. Diarrhea may be intermittent (for months to years) with up to four loose or watery stools per day. Diarrhea is described as foul smelling and is accompanied with frequent abdominal cramps and bowel gas.

Fulminant disease can occur at any time or can be associated with an outbreak of water contamination, although it usually occurs randomly in those at highest risk of disease. For these unfortunate individuals, the onset may be abrupt with high fever (up to 104°F to 105°F), severe cramps, and bloody diarrhea. In other patients, onset may be more gradual, with increasing symptoms over a one- to three-week period. Abdominal tenderness, including hepatomegaly and hepatic tenderness, are frequently seen. It is in these patients that examination of the watery stool for trophozoites is beneficial. If diarrhea is severe, the patient
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should be evaluated for electrolyte imbalance. At the extreme, there may be transmural ulceration of the colon with hemorrhage or perforation, resulting in peritonitis. Less commonly, the organism may be found in other tissues, producing liver, lung, or brain abscesses (Charoenratanakul, 1997; Fujihara et al., 1996; Schumacher et al., 1995). Although some have thought *E. histolytica* infection to be responsible for irritable bowel syndrome (IBS), studies now suggest that this infection is not responsible for that condition (Sinha et al., 1997).

**Diagnosis**

*Entamoeba histolytica* must be differentiated from other intestinal protozoa. Distinction from the nonpathogenic *E. coli, E. hartmanni, E. polecki, E. gingivalis, Endolimax nana, and Iodamoeba bütschlii*, and from the possibly pathogenic *Dientamoeba fragilis* is possible (but not always easy) based on morphologic characteristics of the cysts and trophozoites. *Entamoeba dispar*, however, is morphologically identical to *E. histolytica*, and differentiation must be based on isoenzymatic, immunologic, or molecular analysis. Microscopic identification of trophozoites and cysts in the stool is the common method for diagnosing *E. histolytica* either in fresh stool or stool concentrates. Trophozoites can also be seen in aspirates and biopsy samples submitted to the surgical pathology laboratory.

Immunologic methods exist to identify infection. These techniques are most useful for diagnosing extraintestinal disease where stool examination is not rewarding. Antibody detection kits including indirect hemagglutination, enzyme immunoassay, and immunodiffusion are available commercially. Antigen detection measures are useful to aid the microscopic identification of organisms (Haque et al., 1998; Gonzalez-Ruiz et al., 1994).

**Treatment and Prevention**

Treatment includes both supportive measures as well as medications specifically aimed at eliminating the infection. Supportive treatment includes replacement of fluids, electrolytes, and blood, as needed. Antiprotozoal medications are effective in combination, as some are more effective against infection in the intestine and others are more effective against tissue organisms. Drugs include iodoquinol, paromomycin, diloxanide furoate, and metronidazole.

The mainstay of prevention involves good sanitation and education of those individuals who are at highest risk for infection. Proper food handling, hand

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3See also the CDC website: http://www.dpd.cdc.gov/dpdx/HTML/Amebiasis.htm.
washing, and avoiding potentially contaminated water and food are important. For individuals traveling to areas where there is increased risk of infection, agents exist for treatment of water to kill the infection.

**Correlation with Gulf War Illnesses**

The clinical conditions associated with amebiasis are not the common presenting complaints reported by individuals with undiagnosed Gulf War illnesses, although some of these individuals do have abdominal pain. It is possible, if not likely, that some individuals who served in the Gulf War will have amebiasis given that the infection is common in the United States as well as in most other parts of the world. However, good diagnostic tests for this infection exist; therefore, amebiasis is not a likely candidate to explain the undiagnosed illnesses reported by Gulf War veterans.

**Summary**

Amebiasis is caused by infection with the protozoa *Entamoeba histolytica*. In most individuals, infection is either asymptomatic or produces mild intestinal discomfort. A minority of patients experience serious disease that can include bloody diarrhea and lung, liver, or brain abscesses. The clinical picture is not consistent with undiagnosed Gulf War illnesses.

**SCHISTOSOMIASIS**

**Introduction**

Schistosomiasis, also known as bilharzia, is caused by parasitic worms (trematodes). Infection with *S. mansoni*, *S. haematobium*, and *S. japonicum* cause the majority of illnesses in humans. *S. haematobium* causes urinary schistosomiasis, *S. mansoni* causes intestinal schistosomiasis, and *S. japonicum* causes Asiatic intestinal schistosomiasis. Man is the only important definitive host for the first two species; wild and domestic animals are important reservoirs for the latter. Two other species, *S. mekongi* and *S. intercalatum*, are other important members of this group that cause human disease. Although schistosomiasis is not found in the United States, 200 million people are infected worldwide, second only to malaria in terms of worldwide morbidity and mortality (McCully et al., 1976). The adult worms measure about 1–2 cm in length and live in the venous system of the intestine or urinary bladder.

What is unique to these and other worms is their life cycle. All of these organisms require passage through the snail (*Biomphalaria* sp. for *S. mansoni*, *Bulinus* sp. for *S. haematobium*, and *Oncomelania* sp. for *S. japonicum*) in water to
become infective. They are not passed directly from person to person. The human host releases eggs through the urine or feces into water. In the water, the eggs hatch into the ciliated motile miracidia form that quickly penetrates the body of the snail intermediate host. Inside the snail, the miracidia multiply asexually, and after a period of about 4–6 weeks hundreds of infective motile cercariae emerge. In this form they have a forked tail and the ability to penetrate intact human skin, in part because they release digestive enzymes to facilitate their passage. People wading, swimming, bathing, or washing in contaminated fresh water are at risk. At penetration, the forked tail drops off and the cercaria becomes a schistosomule. This form then migrates into a vessel where it is transported to the lungs and ultimately to the liver. The worms then become sexually mature in the liver venules of man and migrate to their final, species-specific location. Here the worms can live many years and produce eggs that then repeat the above cycle.

**Epidemiologic Information**

Schistosomiasis is present in many parts of the world, including Africa, Latin America, the Caribbean, the Middle East (Iran, Iraq, Saudi Arabia, Syrian Arab Republic, Yemen), Southern China, and Southeast Asia.

*S. haematobium* and *S. mansoni* are both endemic in the Middle East. Historically, the Nile basin is probably the origin of *S. haematobium* and the African lake plateau the source of *S. mansoni* (McCully et al., 1976). It is important to remember, however, that human infection requires a body of fresh water in which the intermediate host snail lives.

**What Infected Patients Experience**

Shortly after infection, the patient may develop a papular rash or cutaneous irritation (schistosome dermatitis), sometimes known as swimmer’s itch. However, most people have no symptoms at this early phase of infection.

The next phase is that of acute schistosomiasis, also known as Katayama fever (rare in *S. haematobium* infection). The patient exhibits fever, chills, cough, asthma, hives, dysentery, weakness, weight loss, abdominal pain, and muscle aches that generally begins two to six weeks following infection (McCully et al., 1976; Rabello, 1995). The acute symptoms, associated with initial egg deposition, diminish over time but may last for several months. Symptoms of schisto-

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somiasis are caused by the body’s reaction to the eggs produced by worms, not by the worms themselves.

Rarely, eggs are found in the brain or spinal cord and can cause seizures, paralysis, or spinal cord inflammation (Pittella, 1997). Long-term complications from infection can result in damage to the infected organs, including the liver, intestines, lungs, and bladder (Shekhar, 1994; Strickland, 1994; Butterworth et al, 1994, 1996; “Infection with schistosomes . . . ,” 1994; Helling-Geis et al., 1996; Hagan, 1996; Morris and Knauer, 1997). Even without treatment, damage to these organs occurs only rarely.

Most patients do well, but there is significant morbidity associated with schistosome infections. The development of periportal fibrosis or portal hypertension can develop over time. Although immunologically mediated, the specifics of this process are not well understood (Cheever, 1997). When studied in patients infected with *S. mansoni*, this process develops over many years. Hepatic function is generally acceptable; patients present with hematemesis or splenomegaly from the portal hypertension. Despite these findings, some patients tend to do better than others with portal hypertension (e.g., alcoholics). In patients infected with *S. mansoni* who develop portal hypertension, glomerulonephritis and cor pulmonale can result in increased morbidity (Nash, 1991).

**Diagnosis**

Because the geographic distribution of this infection is well known, diagnosis starts with a history, looking for travel to endemic areas and exposure to water sources that may be contaminated (Ruff, 1994). The definitive diagnosis is made through examination of feces or urine for the presence of schistosome eggs (Elliott, 1996). A blood test has been developed and is available through the Centers for Disease Control and Prevention; however, the blood must be collected at least 6–8 weeks following exposure to provide adequate sensitivity

**Treatment and Prevention**

Effective and safe drugs are available for the treatment of schistosomiasis (Shekhar, 1994; Elliott, 1996; Brindley, 1994), including praziquantel, which is a broad-spectrum antihelminthic agent. These drugs are usually taken for one or two days, depending on the specific infection.

To prevent infection, individuals should avoid swimming or wading in fresh water in countries where schistosomiasis is endemic. Swimming in the ocean

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and in chlorinated swimming pools is generally thought to be safe. Travelers should avoid drinking contaminated water. Water coming directly from canals, lakes, rivers, streams, or springs should be boiled for one minute or filtered before drinking. Iodine alone is insufficient to eliminate all parasite risk.

Bath water should be heated for five minutes to 150°F. Water held in a storage tank for at least 48 hours should be safe for showering. Vigorous towel drying after an accidental, brief water exposure may help to prevent the *Schistosoma* parasite from penetrating the skin. However, the CDC notes that this may not prevent infection.6

**Correlation with Gulf War Illnesses**

The clinical manifestations and the duration of illness associated with schistosomiasis are quite different from the findings reported among veterans with undiagnosed Gulf War illnesses. Furthermore, although troops were in the Persian Gulf, infection with schistosomiasis requires contact with bodies of fresh water with the intermediate host snails. Only a small number of individuals entered Iraq near the Euphrates River valley, where exposure to schistosomiasis may have occurred (Lashof et al., 1996).

**Summary**

Schistosomiasis is caused by infection with a member of the genus *Schistosoma*. Five different species commonly cause human disease. Schistosomiasis has a complex life cycle that requires an intermediate stage in a specific snail intermediate host. These snails live in fresh water; therefore, human infection can occur only when an individual is exposed to infected water where the snail and the trematode are endemic. Because of the requirement for bodies of fresh water and the difference between the clinical presentation of schistosomiasis and individuals with Gulf War illnesses, this infection cannot be the etiology for symptoms veterans are experiencing.