MILITARY PREVENTIVE MEDICINE: MOBILIZATION AND DEPLOYMENT Volume 2

Section 6: Infectious Diseases of Concern

Franklin Boggs *Pill Call*

Soldiers in the South Pacific theater during World War II get their daily dose of atabrine, described by the artist as "the famous new malaria medicine." Atabrine was used by the allies because Japan controlled the sources of quinine, the main malaria treatment of the pre-atabrine era. The artist also mentioned that "these pills turn you about the color of a lemon." It was the control of malaria that gave General MacArthur of the US Army and General Slim of the British Army an edge in their battles with the Japanese.

Art: Courtesy of US Center of Military History, Washington, DC.

Chapter 35

DISEASES TRANSMITTED PRIMARILY BY ARTHROPOD VECTORS

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MALARIA

Introduction and Military Relevance

Malaria is perhaps the most potentially devastating vector-borne disease for the military. This is because of its ability to appear in a military unit suddenly and cause near universal infection, its ability to incapacitate and kill nonimmune personnel within a few days, and the practical difficulty of controlling infections in tropical garrison units. Service members with even mild cases of malaria often have poor stamina and fitness for any military duties. Malaria is especially a threat for operations in sub-Saharan Africa, the Amazon River basin, Central America, Hispaniola, and much of Southeast Asia and Oceania.

The role of the mosquito in malaria was unknown until 1897 when MAJ Ronald Ross of the Indian Army Medical Department discovered that mosquitoes transmit malaria. Despite this knowledge, personnel deployed to the tropics continue to be plagued by malaria.[1] The age of chemotherapy, using at first the old specific febrifuge quinine and later synthetic antimalarials from the dye industry, offered great promise. Ever-present logistical and discipline problems, however, have been compounded by drug resistance such that the casualty-producing potential of malaria is little different today than it was more than a century ago (Figure 35-1).

Fig. 35-1. This photograph shows a hospital ward in eastern Thailand filled with Thai Marines, all with drug-resistant falciparum malaria. Multidrug resistant malaria can cause mass casualties in service members deployed in the tropics.
Photograph: Courtesy of Colonel G. Dennis Shanks, Medical Corps, US Army.

Burma Campaign, World War II

General William Slim of the British Army had several problems with illness in his troops in 1943 during the Burma Campaign. Nearly a thousand men became ill everyday, and the ratio of sick to combat wounded was 120 to 1, with malaria causing 840 cases per 1,000 men per year. In General Slim's words, "A simple calculation showed me that in a matter of months at this rate my army would have melted away. Indeed, it was doing so under my eyes."[2p177] Several measures turned this unacceptable situation around, and not one of them was primarily medical. Malaria treatment units were moved up into the combat zone so failure to take prophylactic medication only earned a soldier a trip to a field treatment camp and a rapid return to his combat unit. Discipline in taking prophylactic atabrine medication was stepped up, and orders were issued to relieve any commander whose units did not achieve 95% drug positivity measured by unannounced urine testing. Again using General Slim's words: "I only had to sack three; by then the rest had got my meaning."[2p180] Medical support was not enough to win against malaria; command emphasis and discipline were key elements in the victory in Burma (See chapter 2, The Historical Impact of Preventive Medicine in War).

Vietnam War

Malaria was a leading cause of illness in the Vietnam War, with more than 40,000 cases in the US Army alone.[3] In spite of very sophisticated medical care, malaria killed on average one US service member during each month of the Vietnam War. Malaria's impact on combat effectiveness was magnified by two facts: (1) the concentration of cases in the frontline infantry operating in the jungle and (2) drug resistance leading to extended hospital stays. During 1965, entire battalions of the 1st Cavalry (Airmobile) Division were pulled out of the Ia Drang Valley because of malaria casualties exceeding 1% per day.

Somalia

Operation Restore Hope in Somalia (1992-1993) resulted in the largest epidemic of malaria in US military forces since the Vietnam War. Mostly due to noncompliance with the malaria chemoprophy-

laxis regimens (either daily doxycycline or weekly mefloquine), 48 US soldiers and Marines became infected with malaria while in Somalia.[4] Following the redeployment of US Marines to southern California and the 10th Mountain Division to upstate New York, epidemics were noted in both areas consisting primarily of vivax malaria from liver-stage relapses.[5] The risk of vivax malaria was underestimated because of the expectation that Somalia's malaria risk would resemble that of other areas in sub-Saharan Africa. Somalis have Duffy blood group antigen, unlike most Bantu peoples of Africa, and are thus susceptible to vivax malaria. The post-Somalia epidemic of relapsing malaria demonstrated the great need for an easily administered postdeployment medication to eliminate liver-relapse forms of malaria.[6] Despite the importation of malaria into the United States, the risk of resultant locally transmitted cases is small. Malaria, however, remains a very current medical threat to US forces deployed to the tropics.

Description of the Pathogen

Malaria is caused by a genus of parasite known as *Plasmodium*, of which four species are known to commonly infect humans. *P falciparum* is the most important, in terms of the numbers of symptomatic disease and deaths. Both *P vivax* and *P ovale* cause relapsing malaria through their ability to live in the liver in a quiescent form for long periods of time. Relapsing malaria rarely kills. *P malariae* (and *P vivax* less commonly) can cause very long-term bloodstream infections that can be inapparent and are a problem for blood banks because of the possibility of transfusion malaria. All four species are capable of causing human disease noted by fever, chills, headache, sweats, and malaise. The malaria parasite's three separate but interdependent cycles of development take place in the mosquito, the human liver, and the human bloodstream (Figure 35-2). All three cycles are required for the parasite to grow and spread successfully.

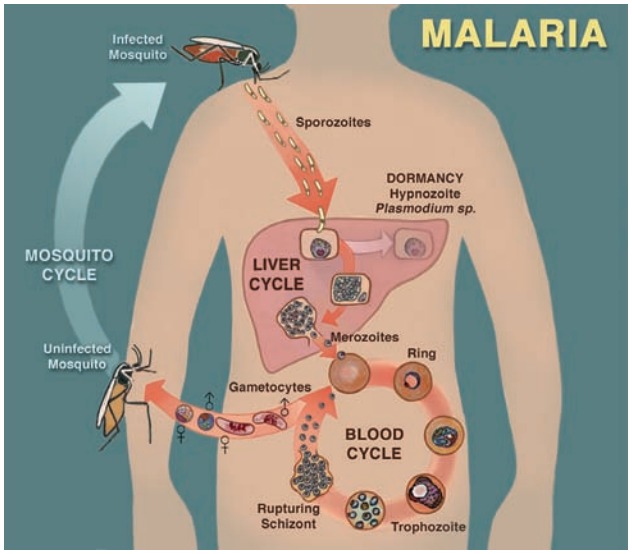

Fig. 35-2. The malaria life cycle.
Art by Annabelle Wright, Walter Reed Army Institute of Research; research by Amelia Pousson.

Mosquito Cycle

The mosquito is not a passive means of transferring infection; the infection must develop inside the mosquito under very precise conditions. Other conditions determine whether a female anopheline mosquito will actually survive long enough to pass malaria to another human. Malaria parasite development in the mosquito ceases entirely when mean temperatures remain lower than 18°C. Those limits determine the season, geography, and altitude that can support malaria transmission. Gametocytes taken from human blood by the mosquito undergo sexual reproduction and eventually become the infective form known as sporozoites in the insect's salivary glands.

Liver Cycle

Sporozoites, the first stage of the parasite, are injected into a human from the mosquito. The sporozoites are rapidly cleared from the bloodstream. Those sporozoites taken up by the reticuloendothelial system are destroyed and do not result in further infection. Sporozoites that make it to a liver cell, however, invade and set up the exoerythrocytic (or liver) cycle. Merozoites develop in the liver and are released into the bloodstream, initiating the blood cycle. When blood parasites seeded from the liver reach sufficient density, symptoms of malaria are induced. The time from mosquito bite to symptoms, called the incubation period, is about 10 to 14 days. Some liver parasites (*P vivax*, *P ovale*) appear to stop their development early in the cycle and thus form a hypnozoite, which appears to serve as the source of malaria relapses months to years later without further infective mosquito bites.

Blood Cycle

The merozoites enter and infect red blood cells and develop into trophozoites (ring forms). These consume hemoglobin and reproduce in the human bloodstream. This cycle of infection is often relatively synchronous and results in regular phases of symptoms, such as chills, fever, and sweats. The diagnosis of malaria is made by microscopic examination of stained blood smears and the detection of the blood forms of the parasite. The rupture of the infected erythrocyte releases factors that can induce symptoms of illness and new parasites (schizonts), which then infect new erythrocytes. Erythrocytes infected with later stages of the parasite (schizonts of *P falciparum*) can bind to the walls of small blood vessels in the brain, lung, and kidney and thus produce lethal infections such as cerebral malaria. Some blood-stage parasites develop into the sexual forms of the parasite in the blood (gametocytes), which serve to reinfect a biting mosquito, thus completing the cycle.

Epidemiology

Transmission

Malaria transmission requires three things: an infected person with gametocytes in his or her bloodstream, an anopheline mosquito to support the development of the gametocytes taken in a human blood meal into the infective form known as sporozoites, and a susceptible person who is bitten by a sporozoite-containing mosquito. Malaria transmission is actually a fragile chain that can be disrupted at several points.[7] In areas of the world with anopheline mosquitoes but without malaria-infected persons, there is no malaria transmission; however, the potential for transmission remains should malaria-infected persons enter the area. This situation currently exists in many parts of the continental United States and in Australia north of about 19° South longitude.

The mosquito itself is usually the weak link in the chain of transmission. Adequately controlling anopheline mosquitoes stops malaria transmission. This worked dramatically well during the malaria eradication campaign of the 1950s and 1960s in marginal areas of transmission using DDT (dichlorodiphenyl-trichloroethane) insecticide. Control of anopheline mosquitoes in the tropics is usually feasible only under special circumstances of limited geographic area and unlimited resources. Protection of the uninfected person is the military's usual method of malaria control. This can take the form of personal protection from mosquito bites (eg, screens, bed nets, repellents) or prophylactic drugs, which suppress the development of malaria infection and symptoms in the service member. Transmission potential in an area can vary widely over time depending on a variety of meterologic and sociologic factors. When efficient transmission occurs, however, infection rates approaching 1% a day have been seen in unprotected personnel participating in night jungle operations.[8]

Malaria can also be spread by blood transfusion and from mother to fetus.

Geographic Distribution

Malaria has a certain expected geographic range which can be predicted from historical records. A quick guide to a country's malaria risk can be found in the Centers for Disease Control and Prevention's annual publication *Health Information for International Travel*.[9] Areas of intense, year-round transmission, often near the equator, are marked by constant warm temperatures and humidity. The vast majority of clinical cases of malaria, especially falciparum malaria, occur in sub-Saharan Africa, the Amazon River basin, and parts of Southeast Asia. Tropical areas free of malaria tend to be urban areas in Southeast Asia and the Americas—areas where effective health services or environmental factors have eliminated the human infection reservoir or areas where deforestation or desertification have eliminated mosquito vectors. Local mosquito information on areas of military interest is often limited and should always be interpreted cautiously because developing countries have inadequate data for military planning, and civil strife usually increases the potential for malaria transmission.

There have been epidemics of malaria recorded as far north as Siberia in the former Soviet Union when summer temperatures allowed transmission to occur, so no fixed latitude lines for malaria transmission can be drawn. Cold temperatures usually limit malaria to altitudes below 1,500 m, but in some areas with population or ecological shifts, malaria transmission can be found in some parts of Africa at heights of greater than 2,000 m.[10] Malaria does not occur in deserts because mosquitoes require a certain amount of water to breed. This water may not be readily apparent, however, and oases in the Arabian Desert are small foci of malaria transmission in a great sea of sand.

Imported malaria refers to cases of malaria in which infection was acquired in another country. In the United States and Europe, most malaria is imported from tropical areas. For physicians treating service members, this presents a particular diagnostic problem if an accurate travel history is not obtained. Imported malaria cases in military personnel represent an extremely small chance of malaria reintroduction to formerly malarious areas because an infection must last at least 2 weeks to have a realistic chance to produce enough gametocytes to infect mosquitoes. This is likely only in an immune individual or one with no access to health care. Most autochthonous cases of malaria in the United States and Europe have been traced to transfusion malaria, relapsing malaria in travelers carrying gametocytes, or "airport malaria" (transmitted by mosquitoes transported in baggage or aircraft from a malarious country).

The most recent example of a military operation causing the reintroduction of malaria from an endemic area into an area that had eradicated the disease is the Afghan War in the 1980s.[11] Large numbers of Soviet military personnel were infected with falciparum malaria. Many of the soldiers were subsequently demobilized and returned to areas of the former Soviet Union, such as Azerbaijan and Tajikistan, that were still potentially malarious despite earlier near-elimination of the disease. At least some secondary spread occurred from the military-associated cases introduced from Afghanistan. A similar incident with vivax malaria was reported in the United States following the Korean War.[12]

Evidence for importation of falciparum malaria via returned military personnel during the Vietnam War is sparse, but veterans did manage to cause a small focal epidemic of falciparum malaria in California by sharing needles to inject illicit drugs. Imported malaria was directly related to military personnel with malaria in 1942 when large numbers of evacuated soldiers from New Guinea caused an epidemic of malaria in Cairns in northern Queensland, Australia.[13]

Incidence

In some locations, the actual risk of new malaria infections varies considerably within fairly small areas. Thai border-guard units stationed only a few kilometers apart on the Thai-Cambodian border had nearly no malaria or attack rates in excess of 1% a day.[14] This example points out the difficulties in making any generalized statements about malaria incidence except that malaria can be very focal. Malaria incidence can be endemic or epidemic.

Endemic malaria is seen in areas of intense transmission, where most of the local population is infected early in life and develop protective immunity to malaria by the time they reach adulthood. Children bear the brunt of malaria disease and deaths, whereas adults usually show low parasitemias with few symptoms. Endemic malaria is usually very stable, and the population shows little disease on superficial inspection. The risk to nonimmune personnel in endemic malaria areas such as sub-Saharan Africa is very high, and particular efforts are necessary to prevent malaria. Missions involving humanitarian support to local populations in areas with endemic malaria require pediatric suspensions for malaria treatment and relatively fewer supplies for adult patients.

Epidemic malaria produces more adult disease than endemic malaria. In areas where malaria transmission is usually low and depends on a conjunction of weather and population factors, most local adults do not have effective immunity to malaria. When malaria transmission occurs, it is unstable and large numbers of adults may die. The Punjab in India is known to have periodic malaria epidemics when the monsoon rains are heavy.[15] Epidemic malaria can also be produced without any climatic changes by population shifts. Large movements of nonimmune service members during military operations or civilians during humanitarian emergencies may introduce a susceptible population into an endemic area, thus producing an epidemic in the newcomers. Epidemic malaria is particularly dangerous in civilian populations because of its ability to overwhelm health care services and confound physicians inexperienced with malaria who confuse it with other febrile illnesses.

In areas that benefited from the global effort to eradicate malaria by spraying dwellings with DDT more than a generation ago, malaria has often resurged following the discontinuation of malaria control efforts.[16] This decay of the public health infrastructure has been widespread and has also hindered malaria surveillance. Sri Lanka nearly eradicated malaria, only to experience its resurgence secondary to the consequences of civil war. Social disruption in North Korean rural areas has lead to some cases of vivax malaria being seen in South Korea. This includes at least 40 cases of vivax malaria seen in US soldiers stationed on the demilitarized zone from 1994 through 1997.[17] Moving semi-immune infected persons from one tropical area to another may spread drug-resistant strains of malaria across the world rapidly.

Pathogenesis and Clinical Findings

Malaria requires a certain incubation period, both in the mosquito before it is infective and in the human until an infection becomes apparent in the blood. The later period, the intrinsic incubation period, is about 10 days for most species of *Plasmodium*. The practical import of this is that very short military operations may not be directly affected by malaria; those sick within the first week of a tropical deployment do not have malaria. The reverse side of this issue is that service members may develop the first symptoms of malaria after returning to areas where the awareness of the disease is often low.

Nonimmune individuals may develop prodromal symptoms of malaria before parasites can be located in a blood smear. The usual clinical findings of malaria include fever, headache, chills, sweats, dysphoria, and mylagia; they have sometimes been described as being similar to a particularly bad case of influenza. In nonimmune persons, this may rapidly progress to severe malaria and death within hours to days. Any service member with a fever who has a travel history within the past year that includes a possible exposure to malaria should promptly have serial malaria blood smears to rule out this very treatable and potentially lethal infection. Although other laboratory signs, such as mild leucopenia, anemia, and thrombocytopenia, are consistent with acute malaria, direct evidence of the parasite must be sought.

Fever

Fever is almost always present when malaria exists in a nonimmune person. Many adults who have become tolerant to malaria through long exposure will have parasitemia without fever, but this situation could serve as an operational definition of malarial immunity. The fever is typically seen in conjunction with the classical triad of the malaria paroxysm: chills, fever, and sweats. The periodicity of malarial fevers is not often noticed if the diagnosis is made and treatment instituted in an expeditious manner. Antipyretics are useful to make the patient feel better because temperatures of up to 40°C are not uncommon. Distinguishing the delirium of high fever due to malaria from early cerebral malaria is nearly impossible and usually unnecessary as both require the same urgent antimalarial treatment.

Anemia

Malaria parasites destroy host erythrocytes, but usually this is not enough to induce anemia unless the infection becomes chronic. Severe anemia, however, is a fairly common finding in young children living in intensely malarious areas. Hyperparasitemia (>100,000 parasites/mm^3) has been treated with exchange blood transfusion to lower the parasitemia, but this approach has not reduced mortality.[18] When frank anemia is seen during acute malaria in a service member, antimalarial drug reactions, such as glucose 6–phosphate dehydrogenase (G6PD) deficiency–induced hemolysis, should be ruled out.

Severe Malaria

Most deaths from malaria within the military are due to failure to consider the diagnosis until the disease has progressed to a severe form. Nonimmune personnel have died after only a few days' illness when adequate treatment was not given quickly. Severe malaria is nearly always caused by *P falciparum* as the parasitized cells attach to small blood vessels in various internal organs.[19] Cerebral malaria appears as a parasite-induced metabolic coma. When treated promptly, patients generally recover full neurologic function, but cerebral malaria is a medical emergency. Analogous forms of severe malaria are seen with renal involvement producing acute renal failure and with pulmonary involvement producing a form of adult respiratory distress syndrome. Both are treated with appropriate physiologic support in an intensive care unit while attempting to kill the parasites as quickly as possible. Parental drugs, such as intravenous quinine (in the United States intravenous quinidine is used), are the keystone of severe malaria treatment.[19] The presence of malaria parasitemia and severe end organ damage does not mean that the two are causally related when dealing with immune adult patients with low parasitemias.

Diagnostic Approaches

The Standard

Thin and thick blood smears are currently the standard for diagnosing malaria. Failure to consider malaria as a diagnosis and to examine microscopically serial thick and thin blood smears is a frequent error noted in the treatment of patients who died of severe malaria in the United States. Small malaria parasites are more concentrated in thick blood smears, where the parasites can look like platelets or other forms of cellular debris. Coloration of stain and patience are important issues when examining blood films. Besides missing actual parasites due

to an inadequate blood examination, false positive results are very common when inexperienced persons examine blood smears for malaria. Pseudoepidemics of malaria have also been caused from over-interpreting normal cellular elements in an effort not to miss a serious treatable disease. Experience in reading blood slides and knowledge of when to obtain a smear are valuable in medical personnel deploying to the tropics.

Newer Diagnostic Tools

In an effort to eliminate some of the subjectivity from the reading of malaria blood films, several new tests to measure parasites in the blood have been developed. They have not yet replaced blood smears, and any military medical unit deploying to the tropics should have the capacity to examine blood films until more experience is gained with the newer antigenic or nucleic acid detection methods. Microscopic examination can be speeded through the use of fluorescent dye in a capillary tube, but this method still requires the ability to interpret microscopically visible parasites.[20] Fixed antigen detection methods using either the histidine-rich protein II or parasite lactate acid dehydrogenase of *P falciparum* have shown promising results and give an answer that is relatively easy to interpret.[21] The usefulness of such techniques in the field remains to be proven. The polymerase chain reaction holds promise as a diagnostic method for a multitude of infectious agents including malaria, but it is still a research tool and is not soon expected to be useful in the field because of the level of technology required for accurate analysis.[22] Rapid diagnostic methods are most likely to be useful in situations where large numbers of samples need to be tested quickly. Until the technology greatly improves, microscopic examination of stained blood films remains the best way to determine if any single service member has malaria.

Recommendations for Prophylaxis, Therapy, and Control

Prophylaxis

Chemoprophylaxis can kill or suppress the parasites, but a continuous concentration of drug must be maintained. Prophylactic and treatment regimens recommended vary over time because of evolving resistance patterns and other factors; it is critical that medical officers consult with command medical authorities to ensure regimens are current (Figure 35-3). The *Health Information for International Travel*[9] and the package inserts of antimalarial medications are also important sources of information regarding issues such as dosage, adverse effects, and contraindications.

Any US deployment into an area with significant malaria transmission requires chemoprophylaxis (Table 35-1). There have been two traditional approaches to chemoprophylaxis during exposure: weekly medication or daily medication. Currently drug possibilities for weekly administration include chloroquine (300 mg base) or mefloquine (228 mg

Fig. 35-3. Two technicians from the Armed Forces Research Institute of Military Science, Bangkok, Thailand, are drawing blood from US Army soldiers of the 25th Infantry Division during the 1988 Cobra Gold exercise in Thailand. The soldiers were enrolled in a malaria chemoprophylaxis trial using mefloquine and doxycycline. Both the Thai and US Armies have been involved in important collaborative work on malaria chemoprophylaxis.
Photograph: Courtesy of Colonel G. Dennis Shanks, Medical Corps, US Army.

TABLE 35-1

DRUGS USED IN THE PROPHYLAXIS OF MALARIA

Drug (Proprietary Name)	Usage	Adult Dose	Pediatric Dose	Comments
Mefloquine (Lariam)	In areas with chloroquine-resistant *Plasmodium falciparum*	228 mg base (250 mg salt) orally, once/wk	<15 kg: 4.6 mg/kg base (5 mg/kg [salt]) once/wk; 10–19 kg: 1/4 tab/wk 20–29 kg: 1/2 tab/wk 30–45 kg: 3/4 tab/wk >45 kg: 1 tab/wk	Contraindicated in persons allergic to mefloquine. Not recommended for persons with epilepsy and other seizure disorders, with severe psychiatric disorders, or with cardiac conduction abnormalities
Doxycycline	An alternative to mefloquine	100 mg orally, once daily	> 8 years of age: 2 mg/kg of body weight orally daily up to adult dose of 100 mg/d	Contraindicated in children < 8 y of age, pregnant women, and lactating women
Atovaquone/ Proguanil (Malarone)	In areas of multidrug-resistant *Plasmodium falciparum*	1 adult tablet daily 250 mg/100 mg orally	11-20 kg: 1 pediatric tablet* 21-30 kg: 2 pediatric tablets* 31-40 kg: 3 pediatric tablets* >40 kg: 1 adult tablet All given once daily	Very well tolerated with some gastrointestinal distress, best given with food
Chloroquine phosphate (Aralen)	In areas with chloroquine-sensitive *P falciparum*	300 mg base (500 mg salt) orally, once/wk	5 mg/kg base (8.3 mg/kg [salt]) orally, once/wk, up to maximum adult dose of 300 mg base	
Hydroxy-chloroquine sulfate (Plaquenil)	An alternative to chloroquine	310 mg base (400 mg salt) orally, once/wk	5 mg/kg base (6.5 mg/kg [salt]) orally, once/wk, up to adult dose of 310 mg base	
Chloroquine + proguanil	A less-effective alternative for use in Africa only if mefloquine or doxycycline cannot be used	Weekly chloroquine dose as above, plus daily proguanil dose 200 mg orally, once daily	Weekly chloroquine dose as above, plus for proguanil: <2 y: 50 mg/d 2–6 y: 100 mg/d 7–10 y: 150 mg/d >10 y: 200 mg/d	Proguanil is not sold in the United States but is widely available in Canada, Europe, and many African countries

* The pediatric tablet is 62.5 mg atovaquone and 25 mg proguanil

Adapted from: Centers for Disease Control and Prevention. Information for health care providers: Prescription drugs for preventing malaria. www.cdc.gov/travel/malariadrugs2.htm. Accessed on May 25, 2001.

base in the United States), and daily possibilities include proguanil (200 mg) alone or in combinations with other drugs or doxycycline (100 mg).[23] Recently daily atovaquone/proguanil (Malarone) has been licensed for daily malaria chemoprophylaxis (Table 35-2). Choice depends on parasite susceptibility in particular regions and other factors.

Weekly prophylactic regimens generally require less effort from the service members. Daily regimens require an enforced administration system, with the drugs typically being given out by squad leaders and supervised by medics. Different armies have favored different drugs for historical and other reasons.[24] Daily administration regimens fail quickly when the drugs are not taken every day because the drugs are eliminated from the circulation in a matter of hours. Weekly administration provides more leeway, but missing a weekly medication dose means that the individual may have a suboptimal drug concentration in his or her blood for several days. Both daily and weekly regimens are usually effective when the appropriate drugs are taken on schedule.

TABLE 35-2

PRESUMPTIVE TREATMENT OF MALARIA

Drug	Adult Dose	Pediatric Dosage	Comment
Pyrimethamine-sulfadoxine (Fansidar) Self-treatment drug to be used if professional medical care is not available within 24 hours. **Seek medical care immediately after self-treatment.**	3 tablets (75 mg pyrimethamine and 1,500 mg sulfadoxine) orally as a single dose	5–10 kg: 1/2 tablet 11–20 kg: 1 tablet 21–30 kg: 1 1/2 tablets 31–45 kg: 2 tablets > 45 kg: 3 tablets	Contraindicated in persons with sulfa allergy
Atovaquone/proguanil (Malarone)	4 tablets taken once daily for 3 days (1000 mg atovaquone/400 mg proguanil)	Daily dose for 3 days: 11-20 kg: 1 adult tablet 21-30 kg: 2 adult tablets 31-40 kg: 3 adult tablets >40 kg: 4 adult tablets	Best taken with food, may cause gastrointestinal distress

Adapted from: Centers for Disease Control and Prevention. Information for health care providers: Prescription drugs for preventing malaria. www.cdc.gov/travel/malariadrugs2.htm. Accessed on May 25, 2001.

Side effects remain a key issue when giving medication to large numbers of healthy personnel. Even minor objectionable drug effects will seriously decrease compliance with the preventive regimen. It is good policy to brief all the medical personnel in depth and inform the service members about side effects and how to counter them. This will also help suppress rumors that occur whenever personnel are placed on mass medication. Doxycycline can cause many gastrointestinal problems, such as stomach upset, when taken on an empty stomach and needs to be taken with food. Women developing vaginitis and light-skinned personnel developing severe sunburn are other problems of doxycycline. Mefloquine can rarely produce serious central nervous system effects, such as psychosis and seizures.[25] Mefloquine is not given to personnel with a history of seizures or serious neuropsychiatric disorders. Flight crews do not take mefloquine because they need to avoid even minor mental problems. More commonly, patients taking mefloquine complain of vague dysphoria. During recent military deployments, there has been a tendency to blame all physical and psychological problems regardless of etiology on prophylactic drugs. The best way to avoid having service members feel that they are being harmed by chemoprophylaxis is to circulate adequate information before starting any mandated medication. This is especially true with primaquine or other postexposure regimens because service members often feel that their risk ends when they leave the endemic area and discontinue taking their medication.

New drugs are under development and can be expected to take their place in the chemoprophylactic universe soon. Azithromycin is a long-acting antibiotic related to erythromycin that may be a substitute for doxycycline. Atovaquone/proguanil has been shown to prevent malaria in Africa and Asia.[26] A long-acting primaquine analog known as tafenoquine is under development and may provide a postdeployment treatment that is easier to use than primaquine. Although used for prophylaxis in some areas of China, the qinghaosu derivatives, such as artemenisin, cannot be recommended for long-term administration.

Treatment

When a nonimmune service member develops malaria, the goal is to bring the parasite count down rapidly to levels where severe malaria is not a consideration and then eliminate the last parasites to effect a cure. Before the development of widespread drug resistance in malaria, one drug (eg, chloroquine) could often perform both functions. Now in many countries, it is often necessary to use one drug to lower the parasitemia rapidly and other, longer-acting drugs to eliminate the last parasites. For severe infections, aggressive treatment in an intensive care unit is indicated. Quinine, or the closely related quinidine, is often used to reduce parasitemia rapidly. Quinidine is the only licensed drug available

to Western physicians for severe malaria.[27] Quinine has a narrow therapeutic ratio and should always be given orally if the patient is able to tolerate oral medication. If oral medications are not tolerated, then quinine is administered via slow intravenous infusion over several hours. Quinine causes a number of objectionable side effects (eg, tinnitus) when given in an adequate dosage and usually causes more problems to the patient than the malaria does by about the third day of treatment. Almost no one will take a 7-day course of quinine unless forced to do so. It is possible that qinghaosu derivatives, such as artesunate, may replace quinine in Southeast Asia, but as of 2000, none of them are licensed compounds in the United States.

Because of the relatively short half-life of quinine and qinghaosu derivatives, it is important to give other drugs to eliminate the last parasites and so effect a parasitological cure. Doxycycline or tetracycline given over the course of 1 week will eliminate residual falciparum parasites. A single dose of mefloquine has been used for the same purpose following a course of artesunate. In some areas where drug resistance has not reached extreme levels, treatment with single-dose drugs such as pyrimethamine/sulfadoxine or mefloquine is still effective. It is unclear how long this situation will last, and all medical officers who treat malaria patients need to be aware that drug resistance is a growing problem that may necessitate longer courses of drugs or combination therapy to obtain cures. If a service member with a previous malaria infection returns within 1 to 3 months of an apparently successful treatment, any reoccurrence may actually be a return of the old infection (recrudescence), which was suppressed but not completely cured. Blood film examinations should be repeated on any individual treated for malaria to ensure that the parasitemia does actually resolve completely.

Postdeployment Malaria

Malaria often occurs in service members after redeployment to nonmalarious areas. This can happen with recrudescence of suppressed infections once prophylactic drugs are stopped or when residual liver stages (hypnozites) cause malaria to relapse long after the initial mosquito bite. The former can be avoided by continuing antimalarial prophylaxis after leaving the malarious area. When using either doxycycline daily or mefloquine weekly, it is recommended that medication be continued for 4 weeks after leaving the malarious area. This is a challenge as personnel often go on leave following major deployments and medication compliance falls accordingly.

Relapsing malaria presents a different problem. Where service members have been heavily exposed to relapsing malaria species (*P ovale* or *P vivax*), it is currently recommended that primaquine (15 mg base daily for 2 weeks) be given to eliminate hypnozites and thus prevent relapses. There is evidence from Papua New Guinea[28] and Somalia[6] that some forms of *P vivax* may be relatively tolerant to primaquine and thus require longer courses using more total primaquine. Primaquine can cause severe hemolysis in some individuals with G6PD deficiency, typically those with ancestors from the southern Mediterranean region and some areas of Southeast Asia and Africa. About 12% of blacks in the US military are G6PD deficient, although their deficiency is usually relatively less severe than that found in other ethnic groups. Testing service members for G6PD deficiency will eliminate most of this risk but involves predeployment testing and accurate recordkeeping. Testing for G6PD deficiency is not done by all military services (as of 2000 the US Army does not), and this must be considered when giving primaquine to large groups.

Much of the primaquine that is dispensed is not taken. Some compliance difficulties may be solved by a new long-acting drug related to primaquine (tafenoquine) under development. Primaquine should be taken with food, as doxycycline is, because this seems to minimize the gastrointestinal intolerance. Blood donors who have had malaria are deferred for 3 years after becoming asymptomatic, donors from countries on the Centers for Disease Control and Prevention's malaria-endemic list are allowed to donate 3 years after leaving the malarious area if they have had no unexplained symptoms suggestive of malaria, and donors who have visited a malarious area are allowed to donate 12 months after leaving the malarious area if they have had no unexplained symptoms suggestive of malaria regardless of their history of antimalarial prophylaxis.[29]

Emergence of Drug Resistance

Prophylaxis and treatment have been severely compromised by the rise of drug-resistant strains of *P falciparum*. When large numbers of persons living in malaria-endemic areas are taking long-acting drugs, such as chloroquine or mefloquine, resistant strains have a significant evolutionary advantage and gradually spread through the population. Since multidrug resistance has now evolved, the situation on the Thai-Cambodian and Thai-Burmese borders is approaching the point where incurable infections can

be anticipated.[30] The current situation in Africa and South America is not so severe, but resistance to both chloroquine and pyrimethamine/sulfadoxine is widespread. Improved access to antimalarial drugs in these areas will inevitably result in further drug resistance. As newer drugs are circulated more widely, more difficult issues of drug resistance can be anticipated. In well-supplied military units, most problems of drug resistance can currently be handled with alternative drugs. This is not the case in many armies from poorer nations, which are now making up an increasing proportion of United Nations peacekeeping missions in malarious areas. A well thought out plan is important to engendering confidence in and compliance with the assigned drug regimens from military personnel.

Some of the islands of Melanesia and Indonesia and some areas of northern South America have chloroquine-resistant vivax malaria. There is no obvious replacement drug for chloroquine in treating relapsing malaria. Relative resistance to primaquine may exist in Melanesia[28] and Somalia based on reports of difficulty eliminating relapses in individuals returning from these areas.[6] Noncompliance, confused orders, inactive or expired drugs, malabsorption, and failure to complete a drug course after returning home are also potential explanations for high malaria attack rates. In vitro analysis of parasite isolates can aid determination of drug resistance evolution, and efforts should be made to obtain blood from problem cases. Most antimalarial drug concentrations can be determined from plasma samples that have been frozen for later analysis to confirm compliance or drug resistance.

Control

Personal Protective Measures. Antimalarial drugs form a vital but not exclusive part of the means of preventing malarial illness. As noted in chapter 22 (Personal Protection Measures Against Arthropods), personal and unit level protective measures are vital to reduce the number of bites from infected mosquitoes and deserve great command emphasis.

Vaccines. Hope that a malaria vaccine might give a simple, durable solution to the problem of malaria prevention in service members became widespread once the molecular nature of malaria antigens began to be uncovered. Unfortunately, no simple fix is in sight.[31,32] Malaria is a protozoan parasite of great complexity that has defied simple immunologic solutions. If and when a practical malaria vaccine comes into use, it will likely include multiple antigens presented with new adjuvants to induce immunity capable of handling the genetic plasticity of plasmodia. Traditional tools of military preventive medicine, including antimosquito measures, chemoprophylaxis, and military discipline, will be needed for the foreseeable future to protect those deployed into tropical regions.

[G. Dennis Shanks, Jerome J. Karwacki]

DENGUE VIRUS INFECTIONS

Introduction and Military Relevance

Dengue viruses are mosquito-borne flaviviruses related to the yellow fever virus. They are responsible for an estimated 20 million to 100 million new infections annually, making them the most common arthropod-borne virus infection of humans.[33] Infection with dengue virus is a prominent cause of febrile illness in tropical areas, where it is known as dengue or breakbone fever. Dengue viruses can cause abrupt epidemics, in which cases of dengue may affect more than 50% of susceptible persons. Since the 1970s, the incidence of new infections has increased in parallel with an exponential rise in abundance of the principal mosquito vector, *Aedes aegypti*.[34] The mosquito species has spread into regions where previously it had been well controlled, most notably in Latin America and the Caribbean region. Increased mobility of human populations has also contributed to the introduction and spread of dengue viruses into many areas of the tropics and subtropics.[35]

Dengue viruses and mosquito vectors pose significant hazards to nonimmune persons when they enter endemic areas.[36] US military populations in particular become exposed to dengue viruses while deployed in tropical regions. Often, sporadic cases occur in service members operating in these environments, but large numbers of personnel may be affected by epidemic dengue if there are favorable entomological circumstances. The continuous prominence of dengue as a common arthropod-borne disease encountered by service members in the tropics has prompted much research, resulting in diagnostic tests and stimulating vaccine development.

The first recorded observation of dengue among US forces was during the Spanish-American War, when troops were stationed in Cuba. During an 8-month period in 1898, 249 cases of clinical dengue were noted, with a case fatality rate of 8 per 1,000

troops.[37] In comparison, yellow fever was observed to be the most prominent disease, with 1,169 cases and a case fatality rate of 123 per 1,000. Dengue was of no importance during World War I as the major American Expeditionary Force campaigns were waged in temperate regions. During the postwar period, classic studies[38,39] in the transmission and pathogenesis of dengue were conducted by Siler and Simmons with personnel garrisoned in the Philippines, where dengue was an immense military health problem. These studies helped identify the arthropod vectors for dengue infection and unequivocally characterized the clinical and hematologic features of the disease.

Dengue was the second most common arthropod-borne infection (after malaria) during World War II, causing an estimated 91,000 cases among US Army forces.[40] Dengue was a particular problem throughout the Pacific, the China-Burma-India theater, and the Mediterranean theaters of operation, where average rates of infection from 1942 to 1945 ranged from 18 to 32 cases per year per 1,000 average strength. Dengue epidemics affecting tens of thousands of service members occurred in New Guinea, Saipan, Hawaii, and other areas (Figure 35-4). Continuous movement of personnel and materiel associated with military operations may also have been related to huge outbreaks of dengue that occurred in ports in Japan, Hawaii, Australia, and many of the Pacific islands.[41]

The major impact of dengue on operations was its propensity to cause epidemics of disease among nonimmune populations taking inadequate preventive measures. Incapacitation of military personnel by

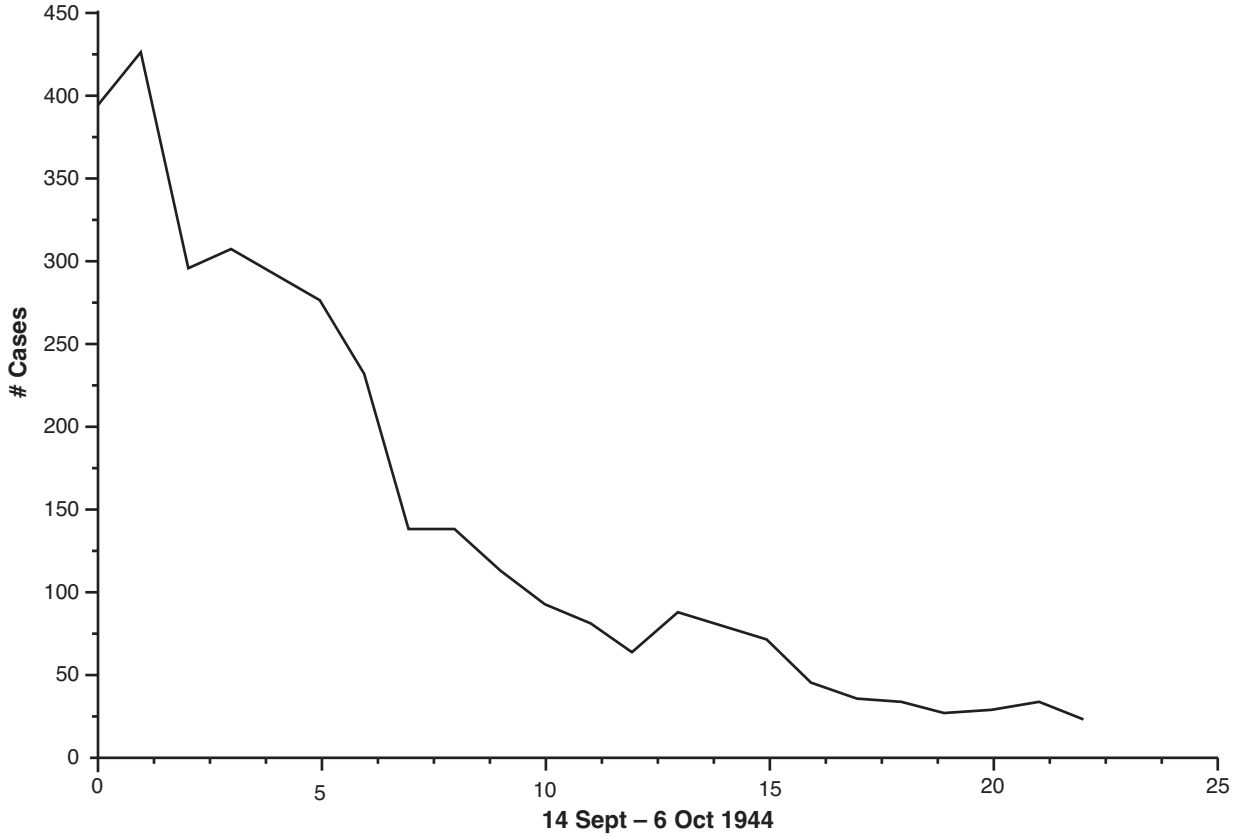

Fig. 35-4. Daily report of new cases of dengue, Saipan epidemic. An explosive outbreak of dengue occurred on Saipan following the assault on the Marianas Islands in June 1944. It was estimated that over 20,000 cases occurred in the most extensive epidemic of dengue during World War II. Rates exceeding 400 new cases per day only decreased after introduction of aerial DDT spraying on 12 September.
Data source: McCoy OR, Sabin AB. Dengue. Coates JB Jr, Hoff EC, Hoff PM, eds. *Communicable Diseases: Arthropodborne Diseases Other than Malaria*. Vol 7. In: *Preventive Medicine in World War II*. Washington, DC: Office of the Surgeon General, Department of the Army; 1964: 39.

dengue during the first weeks of exposure while facing an entrenched and usually immune enemy force was of great concern to commanders. Outbreaks of disease during World War II often were related to combat operations, which complicated mosquito control measures. It was quickly realized that the incidence of dengue was inversely correlated with the effectiveness of the preventive measures imposed by commanders. Epidemics of dengue subsided as rapidly as they arose, generally following institution of vigorous control measures. These included intensification of vector control (eg, destruction of larvae, pesticide spraying, sweeps every 10 days to eliminate containers breeding mosquitoes) and enforced preventive measures (eg, use of personal protection, mandatory use of screened quarters for patients, restricted contact between civilian and military populations). These prevention measures were credited, at least in part, with keeping the rates as low as they were.[37] These policies were pursued to great effect in many regions, and declines in the incidence of dengue in the US Army were seen in all theaters (Figure 35-5).

Many advances in dengue virus research occurred during World War II, primarily due to a team led by LTC Albert Sabin, who later developed oral poliovirus vaccine. Using the Dengue Research Unit at Princeton, NJ, established by the Army Epidemiology Board, Dr. Sabin and colleagues isolated and propagated two serotypes (types 1 and 2) of dengue virus in human volunteers and adapted the viruses to grow in suckling mouse brains.[42] They developed diagnostic tests for each and, using these unique reagents, they characterized immunity to dengue, identified the existence of neutralizing antibodies after infection, and prepared an attenuated dengue virus vaccine.[43] The dengue vaccine was

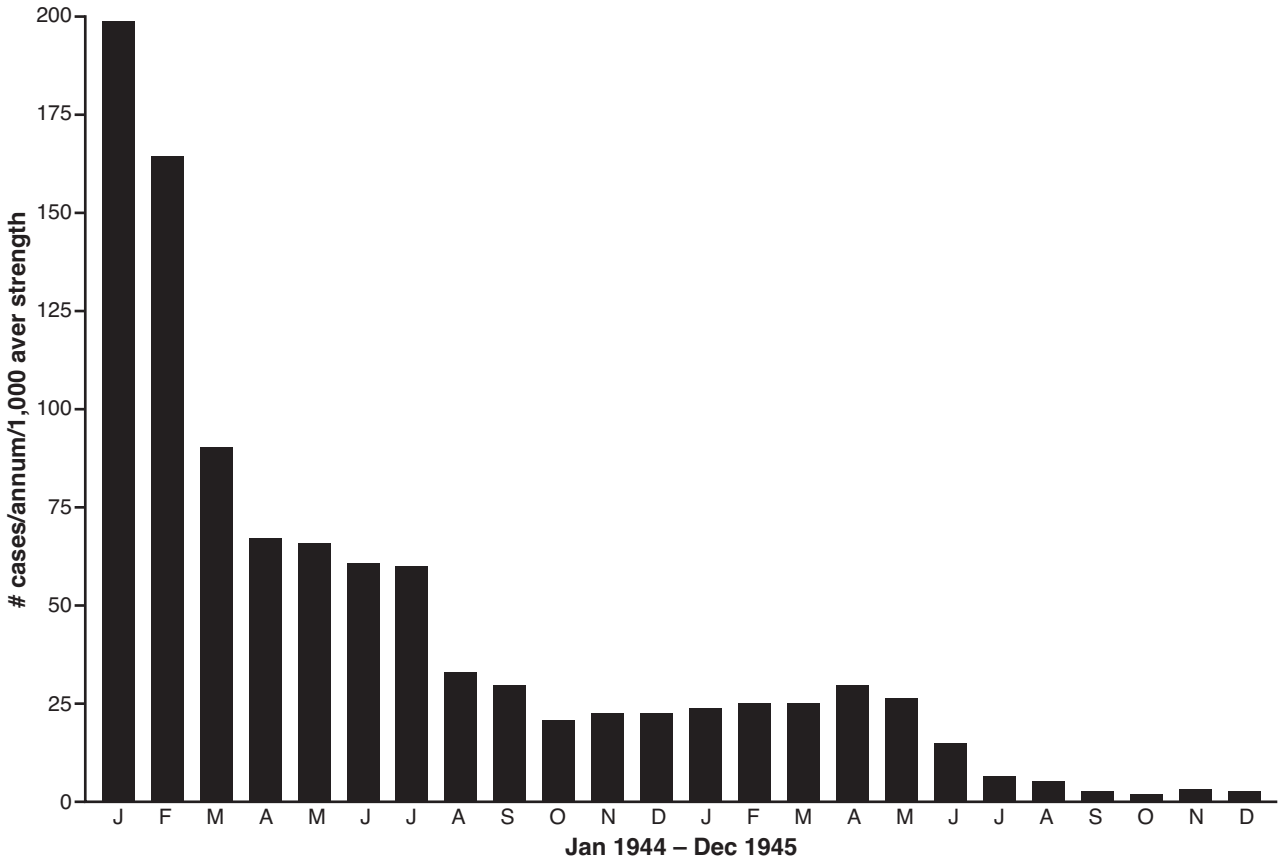

Fig. 35-5. Incidence of dengue in US Army personnel, New Guinea and adjacent islands, January 1944 through December 1945. Epidemic dengue was observed in troops deployed to New Guinea during the rainy season (January-February) 1944. Rates of dengue often exceeded that for malaria in some units. However, introduction of intensive mosquito control and preventive measures, and possibly immunity from the previous epidemic, resulted in lower incidence of dengue in 1945.
Data source: McCoy OR, Sabin AB. Dengue. Coates JB Jr, Hoff EC, Hoff PM, eds. *Communicable Diseases: Arthropodborne Diseases Other than Malaria*. Vol 7. In: *Preventive Medicine in World War II*. Washington, DC: Office of the Surgeon General, Department of the Army; 1964: 37.

tested in volunteers but never administered to personnel in the field, as the war's end interrupted vaccine development.

Subsequent personnel deployments overseas benefited from the lessons of World War II. Increased attention to preventive measures reduced the rate of medical casualties from arthropod-borne illnesses. But as sanitary and personal hygiene were dramatically improved, fevers of undetermined origin (FUOs, febrile illnesses not specifically diagnosed during the 3 days following admission to a military hospital) assumed greater importance as causes of combat ineffectiveness.[44] While dengue did not have a significant role during the war in Korea, the experience of US forces in Vietnam underscored the importance of dengue as a military infectious disease.

Fever of undetermined origin was "perhaps one of the greatest diagnostic dilemmas for military physicians in Vietnam."[45p75–76] It was common—the average incidence rate was 58 FUO cases per 1,000 average troop strength per year (range: 35-100/1,000 per year). Several comprehensive studies documented the etiologies of tropical fevers in personnel deployed to Vietnam; they showed that dengue was the cause of 4% to 28% of all FUOs (Table 35-3). On the other hand, US service members in Vietnam did not suffer major epidemics of dengue "undoubtedly because of the high level of environmental sanitation and the resulting absence of *A aegypti* on most US Army bases in Vietnam. Dengue was contracted mainly by support forces who had contact with civilian populations, as most mosquito transmission occurred in local communities."[41p97] No preventive measures are totally effective in the control of sporadic occurrences of dengue among service members entering an urbanized civilian area.

No dengue occurred during the Persian Gulf War (1990-1991). This may have been due to the exclusion of Coalition personnel from urban areas, the war's occurrence in winter (which decreased vector abundance), and strict preventive measures, including early establishment of disease monitoring and diagnostic laboratory support.[46]

The next major movements of personnel and materiel through the tropics occurred during Operation Restore Hope (Somalia, 1992-1993) and Operation Uphold Democracy (Haiti, 1994-1997). During Operation Restore Hope, more than 25,000 US military personnel were deployed and concerted efforts were made to adopt the preventive medicine lessons learned from the Persian Gulf War.[47] Rates of disease were low, perhaps because of limited contact with the local population. Nevertheless, dengue was responsible for 20% of all febrile illnesses in US military personnel.[48]

Twenty thousand US military personnel were deployed during Operation Uphold Democracy to

TABLE 35-3

DENGUE AS A CAUSE OF FEVER OF UNDETERMINED ORIGIN CASES IN US FORCES IN VIETNAM, 1966-1969

	Study 1	Study 2	Study 3	Study 4	Study 5	Study 6*
Location	93rd Evacuation Hospital	8th Field Hospital	Dong Tam	I Corps (Navy)	12th USAF	9th Medical Laboratory
Dates	4/66 - 8/66	10/66 - 2/67	6/67 - 12/67	2/67 - 9/67	7/67 - 6/68	1/69 - 12/69
# cases	110	94	87	295	306	1,256
			% specific diagnosis			
Malaria	7.0	6.4	12.6	†	70.0	†
Dengue	28.0	10.6	11.0	3.4	5.0	10.4
Japanese encephalitis	1.0	0	1.0	8.1	0	3.9
Undetermined	26.0	38.0	54.0	51.0	12.0	†

* Records of LTC Andre J. Ognibene, from data collected at the 9th Medical Laboratory, Long Binh, Vietnam.
† excluded by study design
Adapted from: Deller JJ Jr. Fever of undetermined origin. Ognibene AJ, Barrett O Jr, eds. *General Medicine and Infectious Diseases*. Vol 2. In: *Internal Medicine in Vietnam*. Washington, DC: Office of the Surgeon General and Center of Military History, US Army; 1982.

Haiti, a known high-risk area for dengue and malaria. In the first weeks of deployment, personnel were located in an urban area close to the local population and to high densities of mosquito vectors. In recognition of the threat of vector-borne disease, service members were given malaria chemoprophylaxis, bednets, and insect repellents. Despite these measures, an outbreak of dengue resulted in significant morbidity and consumption of medical resources.[49] In the first weeks of the operation (from 27 September to 5 November 1994), 112 patients, or approximately 0.1% of US personnel, were evaluated for nonspecific febrile illness. Of a series of 103 consecutive patients admitted to the combat support hospital (25% of all hospital admissions during the period), 30 had confirmed dengue infection.[50] After this initial cluster of cases among personnel centered in the major urban areas, sporadic cases continued to occur. In a 1995-1996 survey of 61 consecutive febrile admissions to a US Army field hospital in Haiti, 25 soldiers were confirmed to have dengue (Sun W. Unpublished data, 1997).

Dengue remains a common cause of sporadic febrile illness in service members deployed to the tropics. However, the explosive spread of dengue virus and vectors throughout the tropics worldwide suggests that the medical threat of dengue may increase in the future, especially when forces are deployed under less-controlled field conditions. Vigilance and adherence to vector control and personal preventive measures will be necessary. Until vaccination becomes possible, sporadic dengue will continue to occur when military individuals must move during daylight hours among civilian populations in endemic areas.

Description of the Pathogen

Dengue viruses are a group of four related viruses, which are distinguished serologically as types 1, 2, 3, and 4.[51] The virus serotypes share 60% to 80% homology at the nucleotide level. All are pathogenic, causing clinically indistinguishable infections in a susceptible human host. Dengue viruses are enveloped 40-50 nm virions that contain single-stranded 11 kilobase RNA enclosed by nucleocapsid proteins.

Epidemiology

Transmission

The vectors of dengue virus are principally urban-dwelling, day-biting, anthropophilic *Aedes* species mosquitoes. The one of greatest importance is *Aedes aegypti.* The vector status of *Aedes albopictus*, the tiger mosquito, remains to be comprehensively established.

Following a 10- to 14-day extrinsic incubation period within an infected mosquito that has fed on an infected person, the mosquito can inoculate virus intradermally whenever it probes into a new host. Dengue virus then infects skin Langerhan cells and migrates to lymphoid organs such as the draining lymph nodes, liver, and spleen.[52] After several cycles of replication, generally within 5 to 7 days after the mosquito bite, dengue virus is detectable circulating in the blood (Figure 35-6). The period of viremia is typically brief (less than 3 to 5 days) and usually coincides with onset of fever and symptoms.

Geographic Distribution

A aegypti is found worldwide and is established in the continental United States. Though *A aegypti* was eradicated from large portions of the Americas, the mosquito returned as control programs waned.

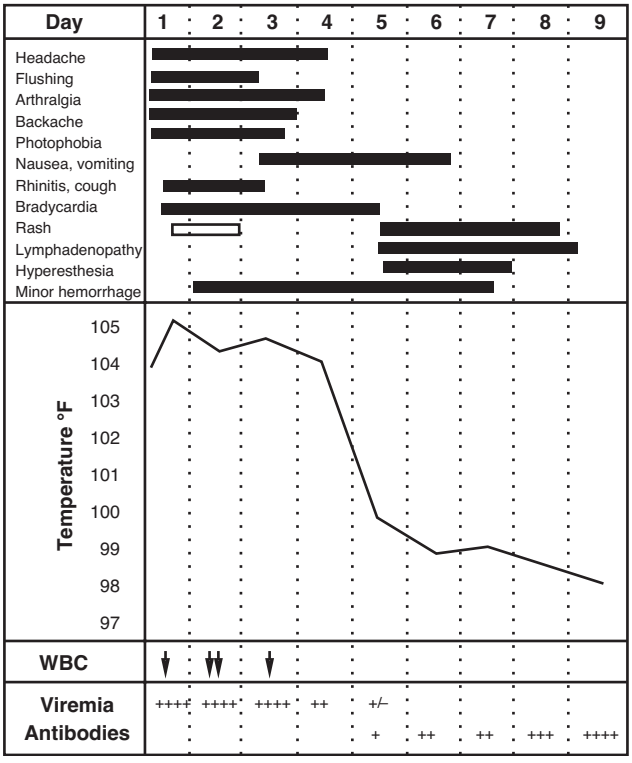

Fig. 35-6. The typical clinical course of dengue fever. Reprinted with permission from: Monath TP, Tsai TF. Flavivirusus. In: Richman DD, Whitley RJ, Hayden FG, eds. *Clinical Virology*. New York: Churchill Livingstone; 1997.

Dengue poses a particular threat to forces deployed in the densely populated urban centers of the tropics, where the disease is often hyperendemic and underrecognized among the local populace. The incidence of dengue virus infections worldwide may be expected to increase in the near future as dengue viruses are introduced into new areas, perhaps even including the southern United States. The increasing pace of short-term deployments to tropical areas may also contribute to increased exposure to dengue.

Dengue hemorrhagic fever (DHF) occurs in areas where three or more dengue serotype viruses circulate simultaneously or sequentially. The disease was first recognized in Asia, but since the 1980s, it has emerged and intensified in Latin America and the Caribbean region.[53] No DHF has been observed yet in Africa.

Incidence

In dengue-endemic areas, infections usually occur in children of preschool and school-age years (peak ages 2 to 9 years) but rarely result in prominent symptoms.

Some infected individuals develop more severe disease with varying degrees of circulatory collapse and hemorrhage (dengue hemorrhagic fever/dengue shock syndrome or DHF/DSS). This occurs in one of several hundred or thousand cases of dengue virus infection.[54] DHF principally affects children younger than 15 years old but may also occur in adults. In all regions where it is found, DHF occurs more frequently, but not exclusively, in individuals with secondary infections with dengue virus.[55] The risk of DHF is increased 100-fold in secondary compared to primary infections in Thailand.[56] Infants with circulating maternal antibodies to dengue virus are susceptible to severe primary infection. The presence of prior immunity to dengue virus poses only part of the explanation for DHF, as severe dengue occurs only in approximately 1 in 200 secondarily infected children.[57]

Dengue-naïve adults traveling to endemic areas are at risk for developing dengue, but their risk for developing DHF appears remote. Despite thousands of cases of dengue in US service members since the 1960s, no case of DHF has been observed. However, if military personnel sustain sequential dengue infections over several years, as children do in areas where DHF is endemic, their risk of developing DHF may increase. Only speculation is possible until the pathogenesis of DHF is fully understood and all risk factors are identified.

Pathogenesis and Clinical Findings

Pathogenesis

Dengue viruses replicate within the cytoplasm of infected cells after receptor-mediated entry. The native receptor on the dengue target cell has not been determined. The known sites of viral replication in vivo are leukocytes, especially circulating B cells, Kupffer cells, and tissue macrophages outside of the neuroaxis. Dengue antigen has been detected by immunofluorescence within tissue macrophages in affected target organs, such as the liver, spleen, kidney, and skin.[58]

Monocytes and macrophages are critical target cells for dengue virus because their infection may be enhanced by cross-reactive nonneutralizing antibody, a phenomenon known as antibody-dependent enhancement (ADE).[59] In ADE, dengue virus binds available group-specific antibody from previous dengue infection and enters the cell through membrane F_c receptors. There is increasing evidence that ADE is important in the causation of dengue hemorrhagic fever.

Coincident with occurrence of fever is a characteristic depression of circulating neutrophil and platelet counts.[60] Infection of dendritic cells by dengue viruses may play an important role in disease pathogenesis.[61] Viremia and fever cease with the appearance of IgM and IgG antibodies to dengue virus (see Figure 35-6). In general, symptoms become most profound as the immune response clears extracellular and intracellular virus. Uncomplicated dengue resolves uneventfully, although some patients experience weeks of convalescent lassitude and asthenia. Rash, pruritis, and acral desquamation can occur up to 2 weeks after defervescence.

Infection with one dengue virus type appears to confer lifelong homologous immunity but little to no heterologous immunity.[62] In many areas of the tropics, three or more dengue type viruses may simultaneously circulate, prompting the occurrence of sequential infections, also termed secondary infections. Secondary infection with a dengue virus has been identified as the major risk factor for DHF/DSS, the most severe manifestations of dengue infection.[57]

The hallmark of DHF is a transient increase in vascular permeability, resulting in a shift of plasma from the intravascular space to the interstitium.[63] When plasma leakage is profound, hypovolemic shock results. It is heralded by hemoconcentration and thrombocytopenia, usually after 3 to 5 days of illness as fever remits.

The body of evidence suggests that monocyte/macrophage interactions with dengue virus are central to the pathogenesis of DHF. Virus entry and replication is probably enhanced by cross-reactive antibody; subsequently, these cells produce cytokines.[64] Complement is activated, generating vasoactive cleavage products C3a and C5a. Immune activation and the resulting cytokine and complement cascade appear to account for the plasma leakage and hemostatic defects that occur in DHF. Conversely, less immune activation in dengue fever accounts for the absence of overt plasma leakage and less severe hemorrhage.

The relative importance of viral virulence in the pathogenesis of DHF is still unclear. Two studies suggest that viruses derived from Southeast Asian genotypes were associated with DHF, in contrast to viruses originating from the Americas.[65,66] Recent data indicate a possible role for viral determinants in severe dengue.[67] As more genetic data becomes available, it is probable that viral factors, and associated host responses, may be key to pathogenesis of DHF.

TABLE 35-4

DENGUE FEVER IN US SERVICE MEMBERS (HAITI, N =55)

Symptoms		
Fever	55	(100%)
Chills or rigors	51	(93%)
Headache/retro-orbital pain	48	(87%)
Nausea or vomiting	36	(65%)
Malaise	35	(64%)
Myalgia	34	(62%)
Diarrhea	21	(38%)
Signs		
Conjunctival injection	29	(53%)
Rash	23	(42%)
Cervical lymphadenopathy	20	(36%)
Laboratory (N = 25)		
Leukopenia (leukocyte count < 3,000/ mm^3)	14	(56%)
Thrombocytopenia (plt<100,000/mm^3)	10	(40%)
Elevated serum transaminases	9	(36%)

Plt: platelet count

Clinical Findings

Adults with dengue have a more overt and characteristic illness than children, prompting some authorities to speak of dengue in adults as "classic" dengue fever. The incubation period is 2 to 8 days. The most common symptoms include abrupt onset of fever (39.5°C-40.5°C), generalized myalgias, arthralgias, malaise, headache frequently accompanied by retro-orbital pain or pain on eye movement, and rash (Table 35-4). Prostration from diffuse bone and muscle pains can be severe (hence the name breakbone fever). Not uncommonly, the patient will experience gastrointestinal symptoms such as nausea, vomiting, bloating, and loose stools. Upper respiratory symptoms are uncommon. An exanthem during the febrile phase is a characteristic yet not pathognomonic finding. It is usually a diffuse, blanching, erythematous macular rash over the trunk and extremities, sparing the palms and soles (Figure 35-7). Less commonly, the rash may be pruritic and evolve to become petechial, morbilliform, or papular and to become associated with desquamation in the digits during convalescence. Symptoms remain intense for 3 to 5 days, then subside rapidly, usually within a week. The patient will occasionally manifest a "saddle-back" fever pattern. The majority of individuals recover and are able to return quickly to normal activity. A few patients, however, may experience prolonged convalescent asthenia. In contrast to this typical adult course, one of the most common presentations in school-aged

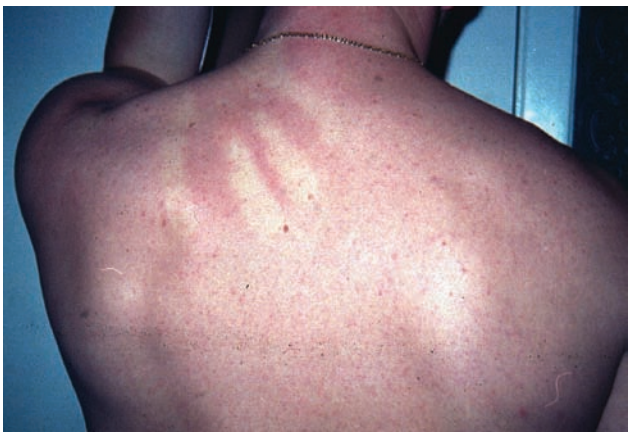

Fig. 35-7. A photograph of a generalized, blanching, erythematous macular rash in a US soldier with dengue fever. The soldier was ill for 2 weeks and took 50 days to return to normal.
Photograph: Courtesy of Amy L. Wyatt.

children in endemic areas is mild fever without localizing signs; many others present with abdominal pain or an upper respiratory syndrome with pharyngitis and rhinorrhea.

Laboratory findings in dengue include transient leukopenia and thrombocytopenia. The drop in white blood cell count is principally due to depletion of mature neutrophils. Occasionally, atypical large lymphocyte forms are also detectable on the blood smear. Elevated transaminases (up to 400 U/L) without rise in bilirubin are seen in about a third of cases; rarely (0.01% to 0.1% of cases), more profound increases in asparate aminotransferase and alanine aminotransferase may be associated with severe liver injury or even liver failure, as is seen in yellow fever.

Diagnostic Approaches

An increase in sporadic cases of fever may be the first indication that dengue transmission has begun in a unit or encampment. The virus has the potential to cause epidemics among exposed personnel. The challenge to the clinician in the acute phase of the illness is to differentiate dengue from other treatable febrile illnesses. Differential diagnosis is complicated by the lack of widely available diagnostic tests and the inability to clinically distinguish dengue from other tropical fevers. It is imperative to exclude malaria, as individuals may be ill with either or both infections. Falciparum malaria is potentially fatal and eminently treatable. Other treatable entities to be considered are rickettsioses and leptospirosis.[68] The hemorrhagic manifestations of dengue may be indistinguishable from yellow fever. It is important to make the distinction because there is an effective vaccine for yellow fever, a disease with 10% to 20% mortality.

The diagnosis of dengue requires laboratory confirmation but should be entertained in any febrile patient having possible exposure who lacks localizing signs and has a normal or depressed leukocyte count. Confirmation of a clinical diagnosis of dengue can be made by identification of virus in blood or by serology. Cross-reactive responses among different flaviviruses complicate definitive serologic diagnosis, though.[69] There are assays currently in use to detect recent or past infection, including hemagglutination-inhibition and plaque reduction neutralizing antibody assays, but these tests are generally unavailable. The most useful diagnostic test is a enzyme-immunoassay for dengue-specific IgM and IgG antibodies.[70]

The presence of detectable dengue-specific IgM or 4-fold rises in IgG titer confirm dengue virus infection. This diagnosis is ideally confirmed by virus isolation and identification with reference antisera. The viruses are best isolated from sera collected from febrile individuals and stored at -70°C prior to shipping on dry ice. Definitive diagnosis of dengue virus infection is most easily achieved from paired sera specimens, one drawn during the acute phase of illness and another drawn at least 2 days after defervescence. Recent experience of deployed US Army personnel in Haiti has shown the limitation of serologic diagnosis.[71] Of 224 serum specimens collected from patients at first evaluation, 58% had no dengue IgM but had positive dengue virus isolation. In the future, nucleic acid detection methods may enable rapid diagnosis even under field conditions.

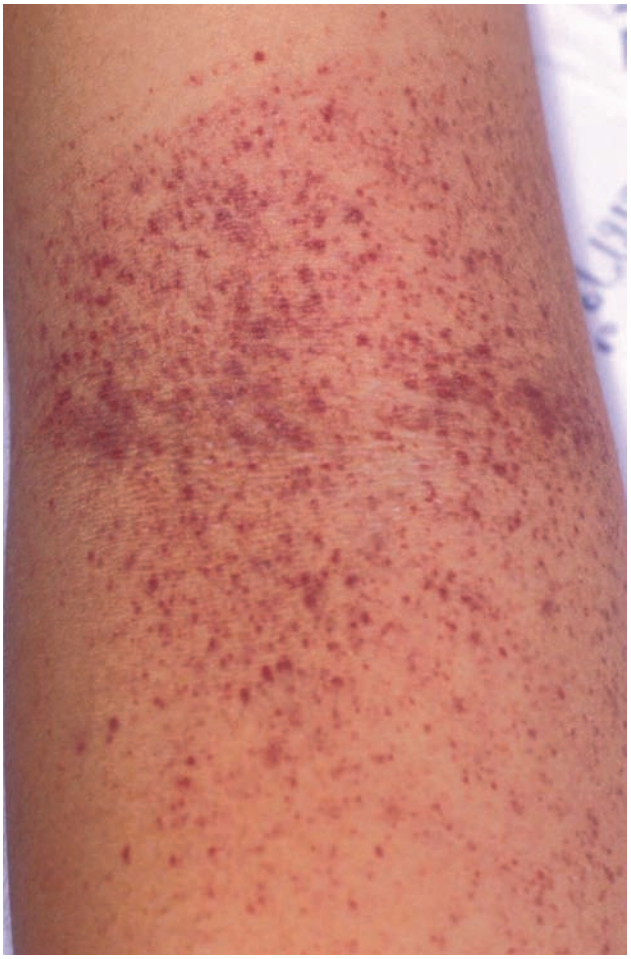

Fig. 35-8. This is a positive tourniquet sign in a patient with dengue hemorrhagic fever from Thailand.
Photograph: Courtesy of Dr. Siripan Kalayanrooj, Thailand.

For the present, a tourniquet test should be performed, as experience in children in Thailand suggests that a negative tourniquet test excludes the diagnosis of dengue infection with greater than 75% certainty after two days of fever.[72] However, a positive tourniquet test is not specific for DHF. The test is done by inflating the blood pressure cuff to midpoint between the systolic and diastolic pressures for 5 minutes and then releasing the cuff. Increased capillary fragility is marked by a shower of petechiae below the cuff. If 20 or more petechiae per square inch are observed, the tourniquet test is positive (Figure 35-8).

The clinician should also be alert to the development of DHF/DSS during the period in which fever remits. The disease starts similarly to dengue but may progress to shock and hemorrhage, usually in the gastrointestinal tract. Warning signs are a falling platelet count (less than 100,000/mm^3) and rising hematocrit. The loss of intravascular volume results in narrowed pulse pressure with tachycardia, hemoconcentration, and evidence of interstitial fluid collection (eg, pleural effusions, ascites). Circulating complement and clotting factors are depleted. In the Cuban outbreak in 1981, the first large outbreak of DHF/DSS in the Americas, the disease in adults was characterized by fever (100%), constitutional symptoms (100%), gastrointestinal symptoms (90%), purpura (66%), and upper gastrointestinal bleeding (40%).[73] Hepatomegaly (35%) and hematemesis (35%) were poor prognostic signs. Laboratory abnormalities of thrombocytopenia and hemoconcentration were seen in 71% and 92%, respectively. Ninety-eight percent of the cases of DHF/DSS in this Cuban outbreak exhibited a secondary antibody response.

There is a continuing need for clinical and laboratory expertise to recognize and treat these infections early, particularly if DHF should occur among previously exposed personnel. Future efforts should concentrate on ways to expedite diagnosis of dengue virus infection and on the development of dengue virus vaccines that offer solid immunity.

TABLE 35-5

TREATMENT AND CLASSIFICATION OF DENGUE AND DENGUE HEMORRHAGIC FEVER

Grade	Symptoms	Signs	Treatment
Dengue fever	Headache, retro-orbital pain, myalgia	Fever (39ºC-41ºC), rash (blanching, erythematous)	-Treat symptoms -Use anti-inflammatory agents (not aspirin) -Monitor clinical status daily -Determine hematocrit & platelet count
DHF Grade I	Same as above	Hemoconcentration (≥20% rise in hematocrit), thrombocytopenia (<100,000/mm^3), positive tourniquet test	Same as above, plus: -Monitor vital signs q 2h, then q 6h -Determine hematocrit, platelet count -Provide oral hydration
DHF Grade II	Same as above	Hemoconcentration and thrombocytopenia, spontaneous bleeding	Same as above, plus: -Type and cross match -Determine PT and PTT
DHF Grade III	Restlessness, confusion, lethargy	Hemoconcentration and thrombocytopenia, rapid weak pulse, narrowed pulse pressure (<20 mm Hg), hypotension, cold clammy skin	Same as above, plus: -Administer isotonic intravenous fluids (rapid 20 mL/kg bolus) -Obtain electrolytes, ALT/AST -Monitor vital signs more frequently (q 30 min or less) -Follow urine output
DHF Grade IV	Depressed sensorium, stupor	Hemoconcentration and thrombocytopenia, undetectable pulse and blood pressure	Same as above, plus: -Administer intravenous colloid or plasma 10-20 mL/kg -Provide critical care support as needed

PT: prothrombin time; PTT: partial thromboplastin time; ALT: alanine aminotransferase test; AST: aspartate aminotransferase test
Reprinted with permission from Kanesa-thasan N, Hoke CH Jr. Dengue and related syndromes. In: Schlossberg D, ed. *Current Therapy of Infectious Disease*. 2nd ed. Chicago: Mosby-Year Book; 2000: 617.

Recommendations for Therapy and Control

Therapy

Dengue is a self-limited illness, and symptoms generally resolve with judicious use of nonsalicylate analgesics and fluids. There is no specific treatment.[74] The treatment of both DHF and DSS is principally supportive, along with close monitoring of hematocrit and blood pressure (Table 35-5). DHF should be suspected in individuals who manifest sudden onset of restlessness, confusion, or lethargy after a dengue-like syndrome. Hospital admission is required for individuals who are at risk for shock, that is, for those who have bleeding, hemoconcentration, narrowed pulse pressure, oliguria, significant prostration, thrombocytopenia of less than 100,000/mm^3, or clinical deterioration. Hospitalization should be considered for other patients who cannot be adequately monitored. Aggressive fluid support can be lifesaving. These measures when used effectively decrease mortality of DHF/DSS to less than 1%.[75]

Control

Efforts to eradicate dengue mosquito vectors have failed, and the vectors resist most conventional control efforts, including ultra-low-volume spraying of insecticides outside homes. Community prevention programs involving removal of fresh water receptacles where the vector may breed and education regarding the habits of the mosquito vectors in the area and the mosquito transmission cycle have had some success. Other available methods for preventing infection involve personal protection using long-acting insect repellents and elimination of local breeding sites. During dengue epidemics, there may be a limited role for insecticide spraying to reduce the density of infected mosquitoes, but traditionally this measure has had little immediate impact. Effective vector control and personal protection measures should be emphasized to military personnel deploying to endemic areas.

The US Army has been a leader in dengue vaccine development, with the goal being a tetravalent vaccine that confers protection against all four dengue serotypes. Since the 1960s, efforts have been made to develop safe, live, attenuated vaccines that would infect and immunize recipients.[76] The pace of vaccine development accelerated in the early 1990s.

[Niranjan Kanesa-thasan, Wellington Sun, Bruce L. Innis]

DENGUE-LIKE SYNDROMES

Introduction and Military Relevance

It is of utmost importance to the clinician and preventive medicine officer to be able to generate a clinical differential diagnosis of diseases that may present like dengue does. This differential will guide the clinician in obtaining the proper sera for a definitive diagnosis and in direct clinical management of potential serious complications such as coagulopathy or shock in the case of the hemorrhagic fevers. This differential will also guide the preventive medicine officer in expanding case definitions of reportable diseases in a theater of operations, as well as the list of potential vectors that may be targeted for vector control. This section will discuss several dengue-like diseases to emphasize the wide diversity of these viruses and their vectors. Since dengue is currently occurring as a worldwide pandemic of the tropical and subtropical regions, the simultaneous occurrence of the viral pathogens discussed in this section and dengue is a very real and valid concern for US service members and their health care providers.

Dengue fever can manifest itself in a broad range of clinical presentations ranging from an asymptomatic infection to a viral syndrome to classical dengue to its severest form—dengue hemorrhagic fever with or without shock syndrome. The differential for a dengue-like disease will change with the nature of presenting clinical symptoms, which themselves depend on factors such as the day of illness, host immunity, and variables that affect immunity (eg, combat fatigue and stress, preexisting immunity, host genetic factors, viral virulence). These factors will generate a continuum of possible etiologies as the disease manifests and progresses in the patient (Figure 35-9).

Oropouche Fever

Introduction and Military Relevance

Oropouche virus was first isolated in Trinidad in 1955 from the blood of a charcoal worker with a febrile illness.[77] A series of epidemics of this disease involving approximately 263,000 persons occurred from 1961 to 1981 primarily in the Amazon River basin but also in the Brazilian states of Manaus, Barcelos, Amazonas, and Amapa.[78] The estimated incidence of oropouche fever during these epidemics ranged from 17 to 60 per 100 persons. From 1961 to 1992, there have been 23 documented outbreaks of

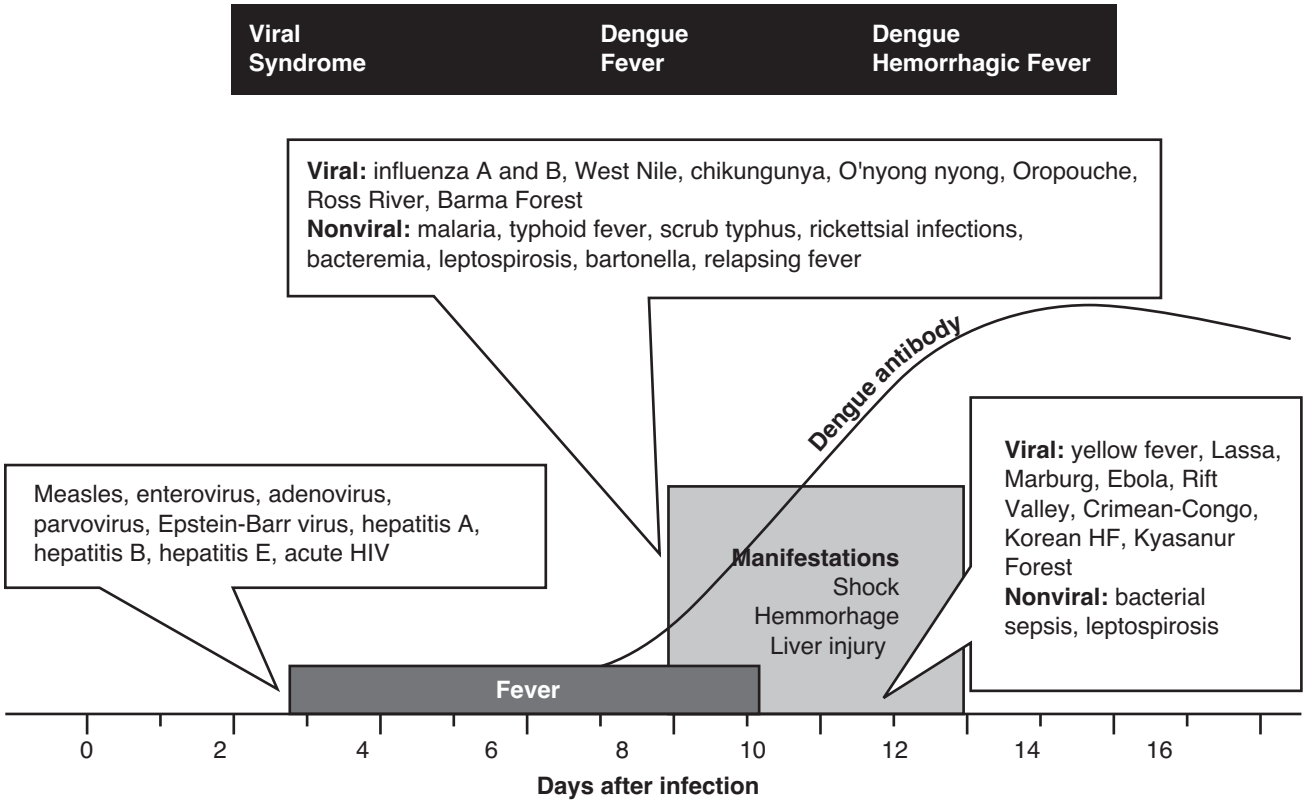

Fig. 35-9. Schema for the differential diagnosis of dengue-like diseases based on clinical dengue illness day.

Oropouche fever in Brazil, 2 outbreaks in Panama, and 1 outbreak in Peru.[79] The wide range of occurrence of this virus throughout the Central and South America, its ability to produce high attack rates among immune-naives, and its high morbidity rate makes this virus militarily relevant for US military personnel deploying into potentially endemic areas.

Description of the Pathogen

Oropouche virus is in the family *Bunyaviridae* and the genus *Bunyavirus;* antigenically it is a member of the Simbu serogroup of RNA viruses.[78]

Epidemiology

It is postulated that Oropouche fever has two cycles of transmission: (1) an epidemic urban cycle in which humans are the primary host and the biting midge *Culicoides paraensis* is the vector and (2) a silent maintenance cycle in which forest animals, primarily sloths, are the primary hosts but the vector is unknown. Recent studies of febrile patients in Panama indicate that Oropouche virus was a common cause of fever and suggests that the virus may be maintained endemically in communities over long periods of time.[79] The endemicity of this disease was confirmed in a cross-sectional serosurvey of a rural community near Iquitos, Peru.[80] The overall seroprevalence of antibody in adults to Oropouche virus in this community was 33.7%; the risk factors for seropositivity were travel to forest communities and travel to Iquitos.

Oropouche fever has been largely reported in the tropics of South America and primarily in northern Brazil. The biting midge *C paraensis* was confirmed to be a potential vector in laboratory studies.[78] The midge, which also is found in Central and North America, feeds readily on humans, breeds in garbage and rotting organic material, and feeds diurnally, with peak blood feeding occurring just before sunset.

Pathogenesis and Clinical Findings

Serosurveys provide an estimate that 63% of persons infected with Oropouche virus will develop clinical manifestations of Oropouche fever.[78] Human disease appears after an incubation period of 4 to 8 days. Viremia occurs during the first two days of illness and is manifested clinically by the sudden onset of fever, headache, muscle ache, joint pains, and photophobia. Leukopenia associated with neutropenia is a common

laboratory finding, although some individuals may have a leukocytosis.[77] Rash is observed infrequently, and other manifestations may be gastrointestinal in nature (eg, nausea, vomiting, diarrhea). Central nervous system involvement can occur primarily as an aseptic meningitis. Infection with Oropouche virus may be teratogenic, based on the teratogenic potential of other related Simbu group bunyaviruses. The illness lasts from 2 to 7 days, and immunity may be life-long.

Diagnostic Approaches

Diagnosis of Oropouche infection can be achieved serologically by standard enzyme-linked immunosorbent assay measuring IgG or plaque reduction neutralization titers. Virus can be isolated during the first days of illness but sera must be stored at -70°C. Oropouche fever in the early stages of disease is clinically indistinguishable from dengue. The absence of rash, hemorrhage, or shock in Oropouche fever are key clinical observations that may distinguish it from dengue.

Recommendations for Therapy and Control

The treatment is supportive, and there is no vaccine for Oropouche fever. Prevention and control of epidemics involve vector control and personal protection measures (see Chapter 22, Personal Protection Measures Against Arthropods).

Rift Valley Fever

Rift Valley fever was first clinically described in 1912 and 1913 in the Great Rift Valley in Kenya. From 1930 to 1931, extensive studies of Rift Valley fever established it as a viral disease that produces illness primarily in domestic animals (especially sheep) but that could produce illness in humans.[81] Further studies elucidated its wide geographic range and demonstrated its potential for fatal outcomes in humans.

Description of the Pathogen

Rift Valley fever virus is in the family *Bunyaviridae* and the genus *Phlebovirus*. Serologic characterization of its antigenic make-up subclasses this virus into the sandfly fever serogroup of the phleboviruses.[82]

Epidemiology

Rift Valley fever virus has been isolated in a large number of blood-feeding arthropods, such as *Aedes*, *Anopheles*, and *Culex* mosquitoes, *Culicoides* midges, *Simulium* flies, and *Rhipicephalus* ticks.[81,83] Transovarial and venereal transmission of the virus has been documented in male and female *Aedes liniatopennis* mosquitoes and may be the mechanism for the maintenance of the virus in the environment. It is postulated that during periods of heavy rainfall, the numbers of infected mosquitoes increase by transovarial amplification, and they spread the virus to susceptible vertebrate hosts, including domestic animals. Rift Valley fever virus can occur naturally in a wide number of animal species, including all domestic animals and such small mammals as mice, rodents, and hedgehogs. In experiments, dogs, cats, rabbits, and monkeys have been infected as well. Animals become a source to infect arthropods, which in turn become vectors, resulting in the escalation of this disease into humans. Risk factors for infection include occupations that demand close contact with animals (eg, veterinarians, butchers, abattoir workers).

Current theory suggests two different types of epidemiologic patterns for Rift Valley fever: (1) epizootics and epidemics occurring in eastern and southern Africa and (2) enzootic and endemic disease in western Africa.[84]

There has been Rift Valley fever activity in 24 African nations. From 1960 to 1978, there have been several isolated outbreaks of Rift Valley fever in Angola, Egypt, Kenya, Namibia, South Africa, Zambia, and Zimbabwe.[81] An outbreak of Rift Valley fever occurred i n Kenya from 1997 to 1998, resulting in more than 80,000 cases.[85] This outbreak is estimated to be the largest reported outbreak in eastern Africa. Phylogenetic analysis of isolates from this outbreak revealed their genealogy to be related to an isolate obtained during the 1990 outbreak in Madagascar. Outbreaks of Rift Valley fever have been characterized by high attack rates in domestic animals, with 30% mortality and an abortion rate of 80% to 100%.[81]

In a study conducted in the northern province of Sudan, 23% of 185 individuals demonstrated antibody to Rift Valley fever virus.[86] In the Nile River delta of Egypt, a seroprevalence of 15% was documented.[87] Cases of Rift Valley fever were not detected in combat troops deployed in during the Persian Gulf War nor was there evidence of infection by postdeployment antibody serosurveys for virus.[88]

Pathogenesis and Clinical Findings

Rift Valley fever in humans is characterized by the onset of fever (which can be saddleback in nature), severe "back-breaking" myalgia, headache,

and anorexia.[81] The illness lasts approximately 4 to 7 days, with viremia occurring in the first 2 days of illness, followed by complete recovery in the majority of patients in 2 weeks. A more severe form of Rift Valley fever can occur and produces ocular hemorrhage with diminished visual acuity, encephalitis, hemorrhagic illness, and death.[84] Ocular Rift Valley fever occurred during an outbreak in Egypt and was characterized by the onset of diminished visual acuity 7 to 20 days after initial symptoms, retinal hemorrhage, and vasculitis. Meningoencephalitis was reported during the South African outbreak in 1975, with the onset of encephalitis 5 to 10 days after the development of fever.[81] Hemorrhagic Rift Valley fever occurs 2 to 4 days after the onset of fever and was the cause of 598 human deaths (case-fatality rates between 0.2% and 14%) during a 1977 outbreak in Egypt and was a feature of the Zimbabwe outbreak in 1978.[81] Outbreaks of Rift Valley fever followed no seasonal pattern but occur after periods of excessive rain or during the development of irrigation projects.[89]

Diagnostic Approaches

Diagnosis of Rift Valley fever can be accomplished by standard viral isolation or molecularly by polymerase chain reaction. Rising antibody titers or seroconversion as detected by enzyme immunoassay or plaque reduction neutralization titers can establish a serologic diagnosis. The clinical distinction between Rift Valley fever and dengue may be difficult, especially if the presentation is a hemorrhagic fever. However, clinically distinct features of Rift Valley fever, such as ocular involvement or encephalitis, and concomitant reports of illness and abortions among local livestock will distinguish Rift Valley fever from dengue.

Recommendations for Therapy and Control

Prevention and control of this disease rely on an active disease surveillance program in domestic animals (as well as humans), immunization of livestock with currently available killed or attenuated veterinary vaccines, and vector control. The effectiveness of antiviral therapy in humans has not been established; however, interferon-alpha and ribavirin have been shown to have protective efficacy in nonhuman primates infected with Rift Valley fever virus.[90] A formalin-inactivated Rift Valley fever vaccine, currently not licensed, has been developed and demonstrated to be highly effective in domestic livestock and in humans.[91] The immunogenicity of the inactivated Rift Valley fever vaccine in humans was recently reviewed.[92] The TSI-GSD-200 inactivated RV vaccine was administered to 540 vaccinees from 1986 to 1997 using three subcutaneous doses at 0, 7, and 28 days. Approximately 90% of vaccinees developed titers of greater than 1:40 of which 98% retained high titers after successful boosting by the vaccines. Of the 10% who were nonresponders, 75% developed antibody titers on boosting with the vaccine. The vaccine was safe and immunogenic, with good long-term immunity after a primary series and one booster dose vaccine. It is available at the US Army Medical Research Institute for Infectious Disease, Fort Detrick, Md. Human vaccination may be indicated for persons at high-risk, such as laboratory or veterinary staff working with the virus or those in areas that are endemic for Rift Valley fever.

Chikungunya

Introduction and Military Relevance

Historically, it has been difficult to distinguish mosquito-borne chikungunya from dengue fever. A number of large outbreaks of "dengue fever" during the 1800s in Egypt, the East African coast, and India were clinically more closely related to chikungunya infection than dengue. The Tanzanian word *chikungunya* was used to designate the severe joint and muscle pains associated with this disease during a large outbreak of clinical disease in that country in 1952 to 1953.[93]

Description of the Pathogen

Chikungunya virus is a positive-sense, single-stranded RNA virus in the family *Togaviridae* and the genus *Alphavirus*. It is antigenically closely related to O'nyong nyong virus.[94,95] Chikungunya virus is genetically highly conserved within Asian and African countries, with parsimony analysis revealing two distinct lineages, one from isolates occurring in western Africa and the other from southern and east Africa and Asia.[96]

Epidemiology

Aedes aegypti mosquitoes in India, Thailand, and Nigeria and *Ae africanus* mosquitoes in Africa transmit chikungunya virus. It has been demonstrated experimentally that these other mosquitoes can carry the virus: *Ae albopictus*, *Ae calceatus*, *Ae pseudoscutellaris*, *Anopheles albimanus*, and *Eretmapodites chrysogaster*.[97] Disease occurs in areas where *Ae aegypti* and *Ae africanus* are present, suggesting that these are the principle vectors for transmission

into humans. Serosurveys of primates have demonstrated chikungunya virus antibody in monkeys, baboons, and chimpanzees, suggesting a possible means of environmental maintenance of this virus.

Chikungunya virus is distributed worldwide. It has produced pandemics in the African nations of Uganda, Tanzania, Zimbabwe, South Africa, Angola, the Democratic Republic of the Congo (formerly Zaire), Nigeria, and Senegal and is endemic throughout sub-Saharan Africa.[98] Chikungunya virus has produced pandemics, and it has become endemic in India and has extended into Southeast Asia including Thailand, Cambodia, and Vietnam. Epidemics of chikungunya fever occurred in the Philippines in 1954, 1956, and 1968; cases of chikungunya fever were diagnosed among US Peace Corps volunteers in the Philippines in 1986.[99] Two large epidemics have been documented in Thailand in 1988 and 1995.[100]

Serosurveys for chikungunya virus in Ibadan, Nigeria, from 1970 to 1974 indicated a seroprevalence of less than 10% in children younger than 1 year of age that increased to 75% by the time the children were 10 to 15 years old. There was an overall seroprevalence of 50% for all ages.[101,102] In Burma, seroprevalence of chikungunya virus antibody ranged from 38.4% in the state of Magwe to 97.7% in Rangoon.[103]

Pathogenesis and Clinical Findings

Human illness from chikungunya occurs after an incubation period of 2 to 4 days, heralded by the abrupt onset of fever and followed in 3 to 5 days by a lymphadenopathy and a generalized maculopapular rash affecting the trunk, limbs, palms, and soles of the feet.[104] A biphasic, saddleback fever can occur and be followed by the development of arthralgia, which becomes a prominent symptom that distinguishes chikungunya fever clinically from dengue fever. Other symptoms include headache, backache, conjunctivitis, and retro-orbital pain. The mortality rate from chikungunya is low, and long-term complications rare. In a study of 107 patients diagnosed with chikungunya 3 years previously, 87.9% fully recovered, 3.7% experienced occasional stiffness, 2.8% had persistent residual joint stiffness, and 5.6% had persistent joint pain and stiffness with effusion.[105]

Diagnostic Approaches

Chikungunya has a higher frequency of rash, conjunctival injection, and arthralgias than dengue fever, and chikungunya's fever ends 2 days earlier than dengue's.[98,104] Chikungunya can manifest hemorrhagic signs (eg, a positive tourniquet test, petechiae, epistaxis) but not the coagulopathy and shock syndrome typical of dengue hemorrhagic fever and shock syndrome. Diagnosis of chikungunya is by viral isolation or serology with complement fixation or neutralization assays. An enzyme-linked immunosorbent assay to immunoglobulin M has been developed that has a high degree of sensitivity and specificity.[106]

Recommendations for Therapy and Control

Treatment of this disease is primarily supportive, and convalescence can be prolonged. A live, attenuated vaccine for chikungunya virus that produces viral-neutralizing antibodies has been shown to be safe.[97] Currently not licensed, it is available at the US Army Medical Research Institute for Infectious Disease. Vector control of this disease involves eliminating the breeding sites for the mosquito and active spraying, as well as personal protective measures.

O'nyong-nyong

Introduction and Military Relevance

O'nyong-nyong was first described in a large epidemic occurring between 1959 and 1962 that started in northwestern Uganda and spread to Kenya, Tanzania, and Zaire; an estimated 2 million people were infected.[98,107] Cases also occurred in the Central African Republic in 1964 and 1965.[98] In June 1996, a disease suspected to be o'nyong-nyong fever was recognized in the Rakai district of southwestern Uganda that spread into the neighboring Mbarara and Masaka districts and in the bordering Bukoba district of northern Tanzania. This was confirmed as o'nyong-nyong virus and documented the first major outbreak of o'nyong-nyong in southwestern Uganda after an absence of 35 years.[108]

Description of the Pathogen

O'nyong-nyong virus is in the family *Togaviridae*, genus *Alphavirus*, and closely related to the chikungunya virus.

Epidemiology

O'nyong-nyong virus has been isolated from the mosquitoes *An funestus* and *An gambiae,* suggesting these as the principle vector for transmission to humans.[109] O'nyong-nyong is widely distributed throughout Africa; serosurveys demonstrate antibody prevalence to o'nyong-nyong virus in Malawi, Mozambique, and Senegal.[98]

Pathogenesis and Clinical Findings

Clinical illness from o'nyong-nyong occurs after an incubation period of more than 8 days and is characterized by the sudden onset of fever (which can be saddleback in character), headache, and severe arthralgia.[98] A viral exanthem can occur, which can be papular or maculopapular. Lymphadenopathy, conjunctivitis, photophobia, myalagias, aphthous stomatitis, anorexia, and epistaxis are other clinical features of this disease. Fever can last for up to 5 days and arthralgia, weakness, and mental depression can be prolonged. No fatalities from this disease have been documented.

Diagnostic Approaches

Laboratory diagnosis is by viral isolation. Serologic confirmation can be made with standard methods; neutralization assays have the greatest specificity. Clinical differentiation from dengue may be made on the basis of joint involvement and absence of hemorrhage or shock syndrome.

Recommendations for Therapy and Control

Similar to chikungunya, treatment of this disease is primarily supportive, and convalescence can be prolonged. Vector control and personal protective measures are the principle means of controlling disease transmission.

Sindbis and Sindbis-like Viral Infections

Introduction and Military Relevance

Sindbis virus was isolated from *Culex* mosquitoes in 1952 in the village of Sindbis, Egypt. Sindbis and viruses similar to Sindbis, termed Sindbis-like, were later reported in parts of Europe, Asia, Africa, and Australia. The potential for causing epidemics in humans was documented during large outbreaks of Sindbis and Sindbis-like viral infections in South Africa in 1974, as well as outbreaks in Sweden, Finland, and the Soviet Union from 1981 to 1984.[110]

Description of the Pathogen

Sindbis and Sindbis-like viruses are RNA viruses in the *Togaviridae* family of the genus *Alphavirus;* antigenically, they are in the western equine encephalitis complex of viruses.[81]

Epidemiology

Sindbis virus has been isolated from a number of mosquito genera, including *Culex*, *Anopheles,* and *Aedes*.[81,111] Virus has been isolated from a number of different birds, suggesting the environmental maintenance of this virus in avian species, with transmission by mosquitoes into humans.

Sindbis-like infection in Sweden, Finland, and the former Soviet Union occurs between the 60th and 64th parallels, with human infection occurring from late July into September and peak incidence in August. It is known by a variety of names (eg, Ockelbo disease, Pogosta disease, Karelian fever).[112] In South Africa, the virus occurs throughout the country, and high infection rates are seen after greater-than-normal rainfall or flooding.[113] In other parts of Africa, antibody prevalence is associated with regions attracting migratory bird populations.

Human infection as described in previous outbreaks occurs primarily in adults between the ages of 30 to 60 years; males are equally at risk for infection as females. Forest exposure is a risk factor for infection.

Pathogenesis and Clinical Findings

The symptoms of Sindbis and Sindbis-like viral infection occur after an incubation period of less than 1 week and include fever, headache, malaise, joint pain, and a maculopapular rash over the trunk and limbs with occasional vesicles.[112] Severe debilitating arthralgias can occur involving, in descending frequency, ankles, wrist, knees, hips, and fingers. The arthralgias can last for up to 3 years. Nonpruritic rash and fever can occur for up to 2 to 3 weeks. No deaths from this infection have been reported.

Diagnostic Approaches

Diagnosis is made by viral isolation and serology (eg, enzyme immunoassay, neutralization titers).

Recommendations for Therapy and Control

Similar to other viruses presented here, treatment of this disease is primarily supportive and convalescence can be prolonged. Clinical distinction of this disease from dengue can be made on the degree of joint involvement, the production of skin vesicles in Sindbis infection but not dengue, and the absence of hemorrhage or shock as can be seen

in dengue hemorrhagic fever. Vector control and personal protective measures are the principle means of controlling disease transmission.

Ross River Disease

Introduction and Military Relevance

Ross River disease, clinically known as epidemic polyarthritis, can produce large outbreaks of rash, fever, and severe polyarthritis. The first report of epidemic polyarthritis was made in 1928 at Narrandera in New South Wales, Australia. The virus was subsequently isolated from a pool of *Ae vigilax* mosquitoes in 1963 near the Ross River at Townsville, Australia. Ross River virus infection is endemic in Queensland, where approximately 300 to 600 cases are diagnosed each year. It has potential to produce large epidemics in other parts of Australia, such as southwest Western Australia and the Murray-Darling River basin. Epidemics have been reported outside of Australia in Papua New Guinea, the Solomon Islands, American Samoa, Cook Island, Fiji, and New Caledonia.[114]

Description of the Pathogen

Ross River virus is in the family *Togaviridae*, genus *Alphavirus*. It is in the antigenic complex of the Semliki Forest viruses, Getah serogroup.[115]

Epidemiology

Ross River virus is endemic in Australia and causes periodic epidemics. The yearly incidence of epidemic polyarthritis in Queensland is 23.6 cases per 100,000 residents. Clinical manifestations of polyarthritis after infection vary between areas that are endemic for disease versus areas that experience epidemics. The incidence of clinical to subclinical infection is estimated to be 1:80 in an endemic area and 1:0.4 in an epidemic area. Ross River virus occurs year-round in central and northern Queensland and during March to June following the summer rains throughout the rest of Australia. The disease occurs most commonly in adults aged 20 to 50 years. Urban-dwelling housewives are more commonly diagnosed with epidemic polyarthritis. There is a positive association between clinical infection and the haplotype HLA-DR7, though no particular ethnic group is at higher risk for infection.[115]

Ross River virus has been isolated from a number of different genera of mosquitoes during the times of outbreaks, suggesting that the mosquito is the major vector of this disease. The virus has been isolated in Australia from *Cx annulirostris, Ae vigilax, Ae normanensis, Ae notoscriptus, An amictus, Mansonia uniformis,* and *Cx liniealis* and in the Cook Islands from *Ae polynesiensis*.[115] During the 1994 outbreak in suburban Brisbane, Ross River virus was isolated from *Cx annulirostris, Cx sitiens, Ae notoscriptus, Ae procax, Ae funereus, Ae vigilax,* and *Ae alternans*. These are peridomestic mosquitoes that breed in fresh and brackish water and may be important during suburban outbreaks.[116] A large number of vertebrate hosts have antibody to Ross River virus, including cattle, horses, sheep, kangaroos, and wallabies, as well as domestic and native birds. None of these vertebrate hosts develop clinical disease nor have any been implicated as a zoonotic reservoir for this virus. This suggests that humans are the principle reservoir during outbreaks, and overwintering of the virus within mosquitoes is the cause for subsequent seasonal disease.[115]

Within the past decade, there have been several large outbreaks of Ross River disease in Australia, raising concerns that the epidemiology of this disease might be changing. From July 1990 to June 1991, there were 368 cases of epidemic polyarthritis in the Northern Territory of Australia.[117] The epidemic started in September and peaked in January, with the highest attack rates occurring in the rural areas and among those 30 to 34 years old. The cause of the outbreak was attributed to higher-than-normal rainfalls and the resultant increase in the mosquito vector. In 1995 to 1996, 540 serologically confirmed cases of Ross River disease were reported in the southwest region of Western Australia.[118] The areas affected were coastal towns and communities in semirural areas and suburbs close to major cities. The changing epidemiology of Ross River virus was examined in a longitudinal questionnaire-based survey of notified cases.[119] The distribution of the disease has changed over time and new areas identified, including the lower Yorke Peninsula, the Flinders Ranges, and metropolitan Adelaide. Symptom severity and duration has increased with recent outbreaks; clinical cases have had a higher frequency of lethargy, tiredness, and arthritis than in past outbreaks and symptoms have persisted 15 months after infection.

Pathogenesis and Clinical Findings

Clinical infection from Ross River virus occurs 7 to 9 days after the bite of an infected mosquito, though a period of up to 21 days has been reported.[120] Arthralgia, arthritis, myalgia, fatigue, and fever characterize Ross River virus disease. Head-

ache, photophobia, lymphadenopathy, and sore throat may occur as well. Rash occurs in over half of clinically ill patients and can occur 11 to 15 days after the onset of arthritis. The rash occurs mainly on the limbs and trunk and is maculopapular but not vesicular in character. Joint involvement is the most common clinical feature and can occur in up to 98% of clinically ill patients; more than half have joint pain lasting greater than 6 months, with some patients experiencing arthritis up to 15 months after infection.[119,120] The rash associated with Ross River virus disease is the result of a cell-mediated immune response to viral antigen within the skin,[115] and laboratory evidence suggests that antibody-dependent enhancement and persistence of virus within macrophages may be a cause of the arthritis.[121]

Diagnostic Approaches

Ross River virus infection can be diagnosed by viral isolation or through molecular techniques such as polymerase chain reaction. Documenting a 4-fold rise in antibody titer by hemagglutination inhibition assay, neutralization titers, or enzyme immunoassay will establish a case of acute Ross River virus infection. An IgM enzyme immunoassay can detect acute cases, though IgM to Ross River virus may persist for months to years.[120] Individuals may develop secondary Ross River viral infection as detected by rising antibodies, but this is not associated with clinical disease.[115] The clinical differentiation of Ross River virus disease from dengue can be made on the basis of the occurrence and persistence of arthritis and the absence of hemorrhage or shock.

Recommendations for Therapy and Control

Therapy for Ross River disease is supportive, with antiinflammatory drugs providing relief from the joint pain.[120] The utility of steroids in relieving joint pain has not been established. Prevention and control of epidemics involve vector control of the mosquito and personal protective measures. A candidate killed-virus vaccine against Ross River virus infection is being developed that has shown immunogenicity in mice.[122] Human efficacy studies have not been performed with this vaccine.

West Nile Fever

Introduction and Military Relevance

West Nile virus was first isolated in the West Nile province of Uganda in 1937. Outbreaks of West Nile disease described in Israel in 1950 involved more than 500 hospitalized patients. Outbreaks recurred each year in Israel from 1951 to 1954 and in 1957.[123] The largest recorded epidemic of West Nile disease, involving several thousands of cases, occurred in the Karoo and southern Cape Province of South Africa in 1974. A subsequent South African epidemic in the Witwatersrand-Pretoria region occurred from 1993 to 1994, with cocirculation of Sindbis virus as a cause of encephalitis.[124]

Description of the Pathogen

West Nile virus is in the family *Flaviviridae*, genus *Flavivirus*. West Nile virus is in the antigenic complex that includes these viruses: Japanese encephalitis virus, St. Louis encephalitis virus, Murray Valley encephalitis virus, Kunjin, Usutu, Kokobera, Stratford, Alfuy, and Koutango.[123]

Epidemiology

Clinical disease from West Nile virus has been reported from countries within Europe, the former Soviet Union, Africa, Southwest Asia, and most recently the eastern United States.[123,125] A serologic survey of West Nile virus in Ibadan, Nigeria, revealed an overall seroprevalence rate of 40% in 304 human sera tested.[126] Both sexes were equally likely to be positive, and there was a higher prevalence in adults as compared to children. In 1990, a serosurvey in Madagascar of 3,177 children between the ages 5 to 20 years revealed an overall seroprevalence rate of 30% to West Nile virus.[127] Seroprevalence rates of West Nile antibody have been reported to be 55% in Karachi, Pakistan,[128] and 32.8% from residents of the Chiniot and Changa Manga National Forest areas of Punjab Province, Pakistan.[129] The cocirculation of Japanese encephalitis and West Nile viruses in fatal cases of encephalitis was observed in the Kolar district of Karnataka, India.[130] The first major West Nile virus epidemic in Romania occurred in 1996 and was characterized by high rates of neurologic complications.[131] During this epidemic, the highest incidence of disease occurred in Bucharest (12.4/100,000), followed by the surrounding districts near Bucharest (1.1-10/100,000). In 835 patients admitted to hospitals with suspected central nervous system infections, 92% met the case's definition for West Nile viral infection, and serologic confirmation was obtained in 352 (80%).

The recent introduction of West Nile virus into

the United States is an example of the continued spread and emergence of the virus into areas previously not thought to be at risk. Since its initial introduction into the New York City area in August 1999, the geographic range of West Nile virus had increased by the end of 1999 to include Connecticut, Maryland, New Jersey, and upstate New York and there were over 60 cases of clinical encephalitis.[132] By the end of the year 2000, West Nile virus was detected in the northeastern United States extending into Maryland and the District of Columbia.

West Nile virus has been isolated only from mosquitoes and ticks.[123] Mosquito species include *Cx antennatus*, *Cx pipiens*, *Cx univittatus*, *Cx perexiguus*, *Ae caballus*, *Ae circulateolus*, *Ae africanus*, *An coustani*, and *An maculipennis*. Tick species include *Argas hermanni*, *Hyalomma asiaticum asiaticum*, and *Ornithodoros capensis*. *Cx univittatus* was the primary arthropod source of West Nile virus isolation during clinical disease in Egypt and South Africa. In southwest Asia, *Cx vishnui* complex mosquitoes, which include *Cx tritaeniorhynchus*, *Cx vishnui*, and *Cx psuedovishnui*, were the primary sources of vector viral isolation.[115] Mosquito surveys and viral isolation during the 1996 Romanian outbreak revealed *Cx pipiens* as the predominant mosquito species in Bucharest. West Nile viral isolation from mosquito pools were all from *Cx pipiens* at a minimum infection rate of 0.3/1,000 mosquitoes.[131] Ticks have not been associated with human disease transmission, and the tick's role in the maintenance or spread of diseases has not been elucidated.[115] Transmission in the New York city area and the eastern United States is thought to be primarily by *Cx pipiens* mosquitoes.[133]

Many vertebrate species have been found to carry antibody to West Nile virus, but only wild birds have been consistently implicated as important hosts in its transmission cycle. Antibody rates of 40% among domestic and wild birds were found in Egypt and 12% in South Africa.[115] In Romania, antibody seroprevalence was 41% in domestic fowl and 8% in wild birds.[131]

The transmission of West Nile virus occurs in two cycles, a sylvatic cycle and an urban cycle. The virus is spread and maintained by migratory birds from Africa and the Middle East. Infected migratory birds then establish a sylvatic cycle, in which virus is maintained and spread by *Cx modestus*, a bird mosquito. Eventually the urban bird population becomes infected, and *Cx pipiens* becomes the primary arthropod vector. An urban cycle is then established, resulting in an epidemic of human clinical disease with humans as the dead-end host and urban birds as the reservoir of the virus.[131] Based on the US experience, black crows have been particularly susceptible to the effects of West Nile virus and have demonstrated a high mortality on infection.[134] Gross hemorrhage of the brain, splenomegaly, meningoencephalitis, and myocarditis were the most prominent lesions.

Because of the migration of infected birds and the mosquito breeding cycle, West Nile viral infection follows a seasonal pattern, with highest transmission activity during the summer months in temperate areas. In Egypt, the highest monthly activity occurred from June to September. In Israel, peak numbers of cases occurred in August to September. In South Africa, outbreaks of human disease occurred during the summer months of December through April.[115] The Romanian outbreak demonstrated a peak incidence of clinical disease between August and September.[131]

Pathogenesis and Clinical Findings

Age does not appear to be important for acquiring infection from West Nile virus, but age is an important determinant of clinical manifestation. Most cases of infection in children are asymptomatic.[115] Symptomatic West Nile viral infection is characterized by the rapid onset of fever that lasts for 5 to 6 days. Other symptoms include malaise, frontal headache, muscle pain, lymph node enlargement, and a maculopapular rash. Convalescence may last 1 to 2 weeks. Neurologic involvement is the most severe manifestation of West Nile viral infection, and the age of the patient correlates to the severity of neurologic disease. During the Romanian outbreak, there was a large proportion of neurologic cases: 40% had a diagnosis of meningitis, 44% had meningoencephalitis, and 16% had encephalitis. The onset of disease was abrupt in these cases, with 91% having fever, 77% acute headache, 57% neck stiffness, 53% vomiting, and 34% confusion. The predominant signs in patients with encephalitis were disorientation, disturbed consciousness, and generalized weakness.[131] Other neurologic manifestations include ataxia, hyptonia, hyperreflexia, extrapyramidal signs, cranial nerve palsies, and seizures. Coma developed in 13% of cases. Case fatality increased with increasing age. No fatalities were observed in patients younger than 50 years, a 3.4% case-fatality rate in those 50 to 59 years old, a 4.3% rate in those 60 to 69 years old, and a 14.7% rate in those older than 70. Among cases of West Nile virus encephalitis in the United States, a mean age of 81.5 years was observed, with common clinical manifestations of fever and muscle weakness.[135]

Diagnostic Approaches

The clinical differentiation of West Nile virus infection from dengue can be made on the basis of the neurologic manifestations and absence of hemorrhage or shock. The differentiation will be difficult for milder cases of West Nile infection and for dengue cases that may manifest neurologic involvement. Diagnosis of West Nile infection may be made using viral isolation during the acute period or viral detection by polymerase chain reaction.[136] Serologic diagnosis can be made by demonstrating a high antibody titer on convalescence or a 4-fold rise in antibody titer by hemagglutination inhibition assay or neutralization titer. Detection of IgM or IgG by enzyme immunoassay can also be performed. Antibody to West Nile virus can cross-react to any of the other flaviviruses, including Japanese encephalitis virus, St. Louis encephalitis virus, and dengue virus. Attempts to confirm clinical cases by viral isolation or polymerase chain reaction should be made in areas that are also endemic for other flaviviruses.

Recommendations for Therapy and Control

Therapy for West Nile viral disease, including encephalitis, is supportive. There is no literature to support the use of steroids in the encephalitis associated with West Nile infection. Control of this disease is similar to other previously discussed arboviruses—vector control through the use of spraying and personal protective measures.

[Timothy P. Endy]

YELLOW FEVER

Introduction and Military Relevance

Yellow fever is a viral zoonosis maintained in nature in monkeys. Humans are an incidental host. The disease was named for the icterus that is frequently present during the illness. Yellow fever occurs in a sylvan, or jungle, pattern and in an urban pattern. Jungle yellow fever is transmitted by arboreal mosquitoes among forest-dwelling monkeys. Human cases occur through incidental contact in the forest with these infected mosquitoes. Urban outbreaks occur when urban-breeding mosquitoes transmit the disease from one infected human to another.

Much of the information here on yellow fever is contained in several excellent reviews on the disease (Exhibit 35-1). Yellow fever was first described as a specific entity in the 1700s. This "bilious fever" was confused with malaria, leptospirosis, and typhoid fever and was thought to be a contagious disease transmitted by miasmas or fomites. Dr. Carlos Findlay proposed the theory of mosquito transmission in 1881.[137] During the Spanish-American War (April–December 1898), the US Army recorded 1,169 cases of yellow fever, and in 1899 the mortality rate was recorded at 21%.[37] US Army Major Walter Reed, working in Cuba in 1900 as president of the Yellow Fever Commission,

EXHIBIT 35-1

RECOMMENDED REVIEWS OF YELLOW FEVER

- Meegan JM. Yellow fever. In: Beran GW, Steele JH, eds. *Handbook of Zoonoses, Section B: Viral*. 2nd ed. Boca Raton, Fla: CRC Press; 1994:111–124. An excellent review article.
- Monath TP. Yellow fever. In: Monath TP, ed. *The Arboviruses: Epidemiology and Ecology*. Vol 5. Boca Raton, Fla: CRC Press; 1989: Chap 51. A fine treatment of the epidemiology of the disease.
- Monath TP. Yellow fever: A medically neglected disease; report on a seminar. *Rev Infect Dis*. 1987;9:165–175. A thorough treatment of current clinical and therapeutic matters.
- Monath TP. Yellow fever: Victor, Victoria? Conqueror, conquest? Epidemics and research in the last forty years and prospects for the future. *Am J Trop Med Hyg*. 1991;45:1–43. A detailed monograph of the history of yellow fever from 1951.
- Monath TP, Heinz FX. Yellow fever virus. In: Fields BN, Knipe DM, Howley PM, eds. *Virology*. 3rd ed. Philadelphia: Lippincott-Raven; 1995: 1009–1016. An excellent review article.
- Strode GK, ed. *Yellow Fever*. New York: McGraw-Hill; 1951. The definitive book on the history of yellow fever and state of knowledge up to 1951.

observed the absence of person-to-person transmission between patients and the nurses caring for them. He disproved the popular theory of fomite transmission by housing nonimmune volunteers in a closed room with soiled linens and clothes from yellow fever patients. None of the volunteers became ill. Reed then demonstrated mosquito transmission by allowing *Aedes aegypti* mosquitoes that had fed on yellow fever patients to feed on nonimmune volunteers. Of 12 volunteers, 10 developed yellow fever. Two volunteers in the same room but separated by a wire screen from the infected mosquitoes did not develop yellow fever.

Reed determined the extrinsic incubation period of yellow fever when he observed that a mosquito could not transmit the disease until 12 days after it fed on a yellow fever patient. Reed later showed that yellow fever was caused by a "filterable" agent in the serum of patients.[138] When volunteers were injected subcutaneously with blood obtained from yellow fever patients, 6 of 7 individuals developed the disease. Filtered, bacteria-free serum from a patient, when inoculated into a volunteer, produced yellow fever. Blood from this second patient, when inoculated into a third volunteer, again produced yellow fever. Reed documented the period between exposure to infected mosquitoes or blood inoculation to the onset of symptoms, the intrinsic incubation period, to be 2 to 6 days.

In February 1901, US Army Major William Gorgas, chief sanitary officer in Havana, instituted measures to control yellow fever based on the findings of Reed's Yellow Fever Commission. By September 1901, yellow fever was eradicated in Havana (See Figure 2-16 in Volume 1).

Yellow fever was originally thought to be an urban disease of humans transmitted only by *A aegypti*, an urban-breeding mosquito. However, in South America rural epidemics were reported where *A aegypti* was not present. In 1932, jungle yellow fever transmitted by forest-breeding mosquitoes was documented. Dynamic mosquito-primate enzootic transmission, composed of wandering epizootic foci in susceptible monkey populations in South America, was finally documented in the early 1940s. A similar jungle cycle was described in Africa during the same period.[139]

Yellow fever epidemics were common in Africa and the Americas through the 17th, 18th, and 19th centuries. Because the disease was thought to be contagious, fear intensified the social disruption caused by the epidemics. During the summer, epidemics occurred along the eastern US seacoast as far north as Boston. Philadelphia had 20 reported epidemics. In 1878, an epidemic in the Mississippi Valley caused an estimated 13,000 deaths. The last US epidemic was in 1905 in New Orleans with 5,000 cases and 1,000 deaths. In Central and South America, vaccination and *A aegypti* control in the 1940s eliminated urban yellow fever, and since then yellow fever incidence has depended on fluctuations in the jungle cycle.[140] Long-term control has been less successful in Africa. In the 1940s in French West Africa, a mandatory yellow fever immunization program was initiated, resulting in control of the disease. The program was abandoned in 1960 and yellow fever reemerged in the area. In English-speaking African countries, control attempts were limited to mass local vaccination campaigns in response to epidemics, and epidemics have continued to occur.[139]

Description of the Pathogen

The yellow fever virus is a single-strand, positive sense RNA virus. It is the first virus characterized of the family later named after it—*Flaviviridae* (from *flavus*, Latin for yellow). This family includes the viruses that cause dengue fever, Japanese encephalitis, St. Louis encephalitis, and tickborne encephalitis. Nucleotide sequencing has identified three geographic topotypes: West Africa (E-genotype IA), America (E-genotype IB), and Central/East Africa (E-genotype II).[141,142] No difference in human pathological response has been noted between yellow fever from South America or Africa.

Antigenic differences exist among yellow fever virus isolates, and some geographic distinctions have been made.[141] Virus isolates from different sources in the same geographic region appear genetically homogeneous and stable over time.[143] All yellow fever strains have been cross-reactive in neutralization tests.[144] There is a close antigenic relationship between yellow fever virus and other flaviviruses found in Africa; some cross-protection is apparent. In monkeys, previous infection with some group B arboviruses was partially protective against subsequent experimental yellow fever virus infection.[145,146] In a yellow fever outbreak in the Gambia, the ratio of inapparent to apparent yellow fever infections was 10 times greater in patients with serologic evidence of a prior flavivirus infection than in the patients with no prior flavivirus infection (22:1 vs. 2:1).[147]

Epidemiology

Transmission

Yellow fever is transmitted only by mosquitoes, not by contact or fomite. In the Americas and in Africa, person-to-person yellow fever is transmit-

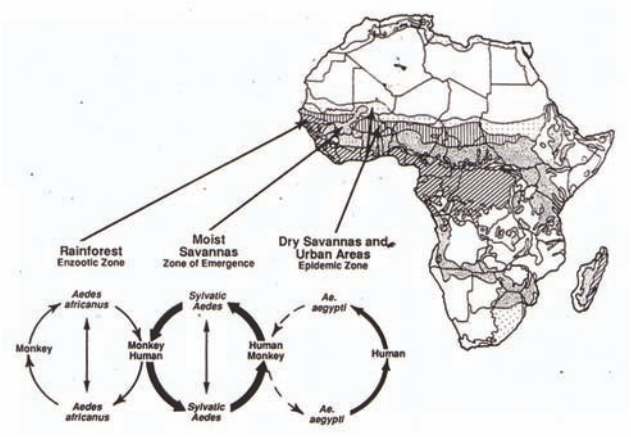

Fig. 35-10. Yellow fever transmission cycles in Africa. Reprinted from: Monath TP. Yellow fever: Victor, Victoria? Conqueror, conquest? Epidemics and research in the last forty years and prospects for the future. *Am J Trop Med Hyg*. 1991;45:30. With permission of the *American Journal of Tropical Medicine and Hygiene.*

ted primarily by *A aegypti* mosquitoes. In South and Central America, jungle yellow fever is transmitted by *Haemagogus* species mosquitoes. In Africa, jungle yellow fever is transmitted by *A africanus* and five other *Aedes* species.[139] In addition, *A africanus* can sustain human epidemics.[148] These transmission cycles are shown in Figure 35-10. A mosquito found in Asia but introduced into the Americas in the 1980s, *A albopictus*, has been shown in experiments to be capable of transmitting yellow fever and is a potential vector for epidemic transmission.[149] There is no evidence for transmission by *Culex* species mosquitoes. *Amblyomma* ticks in Africa have been shown to harbor yellow fever virus, but their role in transmission has not been defined.[140,141]

Blood from a yellow fever patient is infective for a mosquito shortly before the onset of the human's fever and up to 5 days afterward. The virus incubates in the mosquito for 9 to 12 days (the extrinsic incubation period), after which the mosquito remains infected for life. There is evidence that yellow fever virus can be transmitted transovarially in mosquitoes in Africa.[150] This, along with the prolonged survival of adult mosquitoes, may account for maintenance of the virus during the dry season.

In the rain forest, vector mosquitoes (*A africanus* in Africa, *Haemagogus* species in South America) remain high in the tree canopy. Humans do not often come in contact with these mosquitoes unless the trees are being or have recently been cleared. In less-dense forests in climates with dry seasons, these mosquitoes are more active at ground level. Biting intensity is high during the wet season and nearly absent during the dry season. *A aegypti* mosquitoes breed in areas of human habitation and bite during the day. As a result, human contact with these mosquitoes is almost constant.

In Africa, yellow fever patterns depend on vegetation and rainfall patterns, which influence the population of mosquitoes and primate hosts. The equatorial rain forest of West Africa is a zone of low-level enzootic transmission. The surrounding zone of forest and savannah with cyclic rainy and dry seasons can sustain high transmission rates because of its abundant vector and primate populations. A high level of jungle transmission may occur without human cases if the human population is small or there is a high prevalence of vaccine-induced immunity. The junction of mixed savannah-forest and savannah is the "emergence zone" that allows the annual sylvatic amplification of the virus during the rainy season and repetitive infections in the human population living in the area.[141] Most outbreaks in sub-Saharan Africa occur during the late rainy season and the early dry season (September to December), although an urban outbreak occurred in 1987 in western Nigeria during the late dry season (April to May). This outbreak was thought to be due to high concentrations of domestic *A aegypti* mosquitoes and an earlier sylvatic outbreak nearby.[148] In the tropics of the Americas, the incidence of jungle yellow fever is highest during the months with the greatest rainfall: January to March.[141]

In urban areas or the savannah areas with a prolonged dry season, sylvatic mosquito populations are too low to sustain a sylvatic maintenance cycle. Therefore transmission to humans is absent and the prevalence of immunity in humans is low. These regions have the highest risk for epidemic (urban) yellow fever.

Sylvatic yellow fever transmission may be a "wandering epizootic" because the monkeys that survive infection are immune for life. In South American primates, several species develop fatal infection and several years are necessary for the population to redevelop. In Brazil, yellow fever appeared in monkeys every 7 to 10 years, an interval similar to that found for human yellow fever in that country. Few African primate species develop fatal infection. Because the primate population is not decimated, a larger population of susceptible individuals can accumulate in a shorter time and may account for the shorter interval between periods of yellow fever typical in Africa.[140]

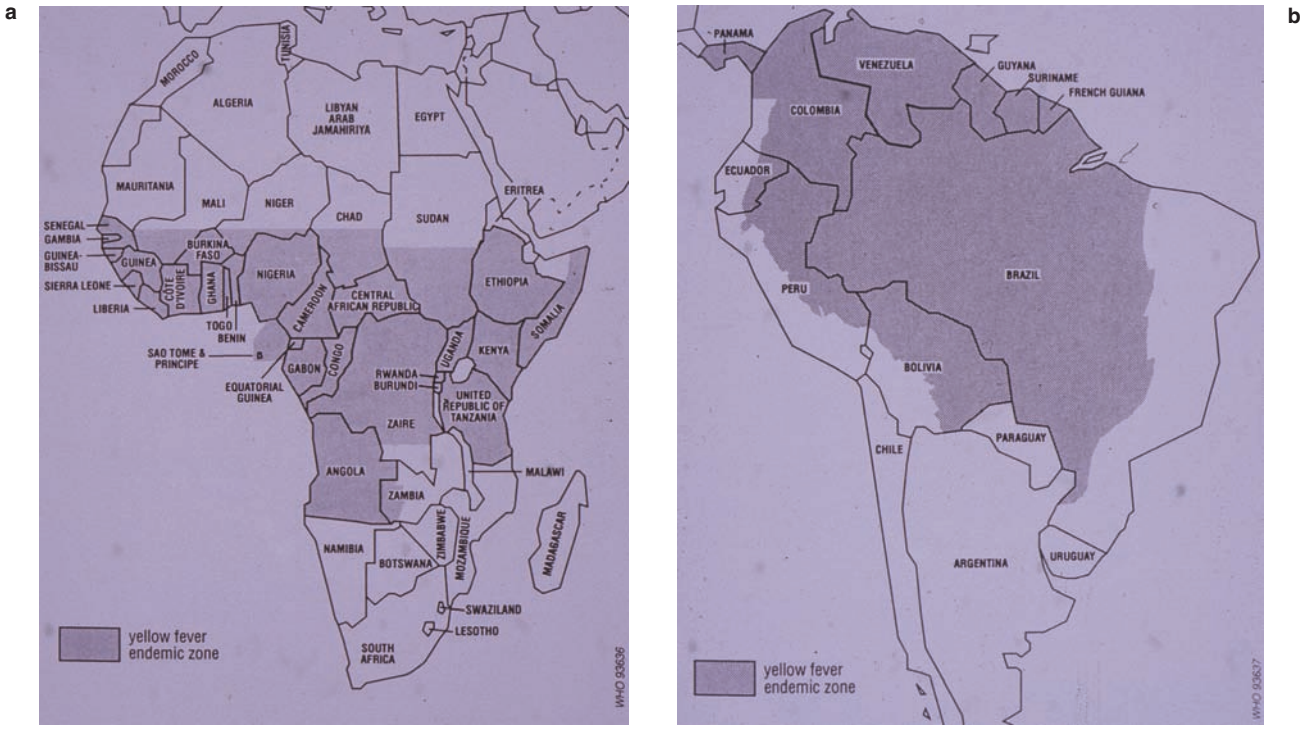

Fig. 35-11. The Yellow Fever Endemic Zones in Africa (*a*) and the Americas (*b*).
Reprinted with permission from: World Health Organization. *International Travel and Health: Vaccination Requirements and Health Advice*. Geneva: WHO; 1996; 14, 15.

Geographic Distribution

Yellow fever occurs in tropical areas of Central and South America and from 15° North latitude to 10° South latitude in Africa (Figure 35-11). In South America, 95% of yellow fever cases occur in the rain forests of Peru, Bolivia, Colombia, and Brazil. Since the last urban case of yellow fever occurred in Trinidad in 1954, all this transmission had been forest-related.[140] *A aegypti* populations have expanded in South and Central America since the early 1980s, creating potential for the recurrence of urban epidemics, and urban cases have recently been reported in Bolivia.[151] For reasons that are not clear, yellow fever is absent in Asia, despite the widespread distribution of *A aegypti* mosquitoes there.

Incidence

The age distribution of yellow fever patients depends on the prevalence of immunity in the population from prior epidemics and vaccination campaigns. In urban yellow fever in endemic areas the greatest incidence is in children; they account for up to 73% of cases. Jungle yellow fever in the Americas is most common in young adults, due to occupational exposures. Yellow fever incidence from 1986 to 1990 was the highest reported to the World Health Organization (WHO) since official reporting began in 1948, with 17,728 cases worldwide and 4,710 deaths; 16,782 of the cases were in Africa.[139]

Pathogenesis and Clinical Findings

Most of the knowledge of the pathogenesis of yellow fever is based on findings in experimentally infected rhesus monkeys.[152] Virus in the saliva of the infected mosquito replicates in cutaneous tissues of the animal at the site of inoculation and in local lymph nodes. The virus then spreads hematogenously to the liver, spleen, bone marrow, and cardiac and skeletal muscle. The liver is the primary organ affected, and hepatocellular injury is due to the direct effect of the replicating virus. Replication is in the cytoplasm, with release of particles by cell lysis. Inflammation is minimal or absent. Hepatic histopathology shows swelling and coagulative necrosis of hepatocytes but inflammatory cellular infiltrates are minimal. Histopathologic findings are not specific for yellow fever, and liver biopsy is contraindicated because of

the high risk of hemorrhage. After recovery from yellow fever, there is no evidence of residual damage.[153] Renal glomerular changes are mild and the cause is unclear. Renal injury appears to be due to prerenal impairment with subsequent acute tubular necrosis.[152,154,155] The virus appears to injure the myocardium directly, but there is no evidence of direct viral injury to the brain[155] or the lung.[153] Subsequent clinical complications result from liver, renal, and cardiac dysfunction and may include acute renal failure, acidosis and shock, myocarditis, disseminated intravascular coagulation (DIC) and hemorrhage, and encephalopathy.

Yellow fever is an illness of acute onset, short duration, and variable severity. The clinical course has been divided into three phases: infection, remission, and intoxication. The onset of yellow fever, the period of infection, is characteristic but not specific for yellow fever. Symptoms appear after an incubation period of 3 to 6 days, and a prodrome is usually absent. Usual manifestations include the abrupt onset of fever, headache, myalgia, lumbosacral pain, nausea, malaise, and weakness. During this phase, the patient is viremic and infectious to mosquitoes. Associated findings include apprehension, an initial rapid, bounding pulse followed by a relative bradycardia (Faget's sign), conjunctival suffusion, flushing of the head and neck, reddening of the edges of the tongue, minor gingival hemorrhage, and occasional epistaxis. This first phase lasts approximately 3 days. In abortive infections, these symptoms resolve and the patient recovers. In the mildest infections, the patient may have nothing more than a transient fever and headache, which resolves in hours.

In more severe cases, the period of infection is followed by a brief period of remission. This lasts up to a day, during which the patient's symptoms improve, but then the blood pressure falls and there is a return of fever, vomiting, and prostration. These events mark the onset of the period of intoxication, during which the patient may develop severe yellow fever's classic triad of findings of jaundice, hemorrhage, and intense albuminuria.[156] In this phase, there is no viremia and antibodies appear. Some patients may recover in 3 to 4 days, but 50% of patients who enter this phase die, usually at 7 to 10 days, with hemorrhage, shock, encephalopathy, and renal failure. Jaundice is of variable severity and often not prominent. Hypothermia and delirium progressing to coma are terminal findings. Findings that indicate a fatal outcome include rapid progression to the period of intoxication and rapid rise in the serum bilirubin, severe hemorrhagic diathesis and DIC, acute tubular necrosis, early hypotension, shock, coma and convulsions, and intractable hiccoughs.[155] Signs of a good prognosis include diuresis and normal mental status.[156]

Laboratory findings include early leukopenia with neutropenia, thrombocytopenia, liver transaminase and bilirubin elevations; proteinuria; azotemia; and coagulation defects (prolonged prothrombin time and partial thromboplastin time) suggesting DIC. Electrocardiogram findings are nonspecific and may show prolonged PR and QT intervals and ST abnormalities. Hepatic transaminase levels rise on the second or third day, peak 2 to 5 days later, and decline over the next 2 weeks, although mild elevations may persist for 2 months. The degree of transaminase elevation indicates the severity of the disease and the prognosis.[155] Alkaline phosphatase levels remain near normal. Cerebrospinal fluid has increased pressure, elevated protein, a normal cell count, and normal glucose levels.

Complications include suppurative parotitis, bacterial pneumonia, sepsis, and acute tubular necrosis. Atypical fulminant cases may cause death in 3 days, occasionally without hepatic or renal signs. Convalescence may take 1 to 2 weeks. Late deaths may occur after weeks and are attributed to myocardial dysfunction or dysrhythmias. Recovery is usually complete, but jaundice can persist for months.

The differential diagnosis in the early period of infection is broad and must include other arboviral diseases, malaria, rickettsial infections, leptospirosis, typhoid fever, and viral hemorrhagic fevers. During the period of intoxication, the appearance of jaundice makes the diagnostic considerations viral hepatitis, leptospirosis, malaria, typhoid fever, and other viral hemorrhagic fevers. The high case fatality rate in yellow fever, often more than 30% in hospitalized cases (compared to viral hepatitis where the case fatality rate is usually less than 1%) can be valuable in the differential diagnosis.

Yellow fever has characteristic findings, but they are nonspecific and nondiagnostic. Therefore, a clinical diagnosis of yellow fever is not indicated except in the setting of a documented outbreak. In an outbreak, fever and jaundice are often used for case identification.[147] Other diagnoses must remain in consideration until the laboratory diagnosis of yellow fever is made. In a patient with hemorrhagic manifestations, viral hemorrhagic fever must be considered and appropriate infection control precautions taken until a definitive diagnosis is made. Because treatment for yellow fever is supportive only, severe diseases that can be treated, such as malaria and typhoid fever, should be considered first and if diagnostic tests cannot be performed, empiric and possibly lifesaving therapy should be considered.

Subclinical, or inapparent, infection is common. The ratio of infections to clinical cases ranges from 2:1 to 20:1. In a Gambian epidemic in 1978, 33% of the population showed serologic evidence of infection, and the overall clinical-to-subclinical infection ratio was 1:12.[147] Antibody appears within the first week, and recovery confers lifelong immunity. In infants, passive immunity persists up to 6 months after birth.

Diagnostic Approaches

Yellow fever can be diagnosed by detecting the virus in blood or liver biopsy specimens or by detecting serum antibody specific for the yellow fever virus. Because of the danger of hemorrhage, liver biopsy is absolutely contraindicated in the living patient. Detection of the virus or viral antigen in the blood is the most specific diagnostic method. Viremia is greatest 3 to 6 days after the onset of the illness but has been detected as late as day 17. The virus can be isolated by inoculating the patient's blood into suckling mice, mosquitoes, or mammalian or mosquito cell culture. Viral antigen can be detected in blood by enzyme immunoassay (EIA)[157] and in tissue by labeled antibody binding. Viral genome can be detected by polymerase chain reaction (PCR) amplification.

Acute yellow fever can be diagnosed by detecting IgM specific for the yellow fever virus in a patient with a compatible illness or during an outbreak. IgM develops within the first week of the infection, persists for months, and is the target of the serologic test of choice to diagnose acute infection. Acute infection cannot be diagnosed by detecting IgG in a patient with possible previous yellow fever infection or in a person vaccinated against yellow fever, except when a significant rise in the IgG titer in convalescent serum compared to acute serum indicates acute infection. Cross-reacting antibodies due to other flavivirus infections are difficult to distinguish from antibody due to acute infection. This distinction can sometimes be made using a yellow fever type-specific antigen EIA and other serologic tests, such as hemagglutination and complement fixation.

For laboratory detection of yellow fever virus, blood specimens must be obtained from the patient during the first 3 to 4 days of the illness and a postmortem liver biopsy specimen must be obtained within 12 days after the onset of the illness. Specimens for virus detection, such as blood or liver tissue, should be kept at 4°C or on wet ice if they can be delivered to a laboratory within 48 hours. If they must be held longer, they should be frozen on dry ice or in liquid nitrogen. Standard refrigerator freezer temperatures will cause deterioration of the virus. If refrigeration or freezing is not possible, the specimen should be placed in a 50% glycerol solution and shipped at ambient temperature.[158] Virus can be detected in cell culture after 3 to 4 days, while EIA and PCR results take less than a day.

Recommendations for Therapy and Control

Therapy

Therapy consists of symptom control and support only. Ribavirin has some antiviral effect but showed no clinical benefit in experimentally infected monkeys.[141] Interferon gamma showed some benefit if initiated before organ injury occurred.[154] Hypotension and hypoxemia should be managed aggressively. The PTT (partial thromboplastin time) should be kept under 30 seconds using fresh frozen plasma. The value of heparin for DIC is unclear. Nonaspirin antipyretics should be used. Prerenal azotemia should be managed aggressively. Sepsis and bacterial pneumonia must be diagnosed early and treated promptly. There is no evidence to support use of corticosteroids. Immune serum may be protective if given immediately at the time of infection, but it has no effect after the disease appears.[144] Routine blood and body fluid precautions should be used, and the patient must be protected from mosquito access for at least 5 days after the onset of symptoms.

Control

Suspected yellow fever patients should stay inside bed nets or screened rooms to avoid further transmission. The patient's house and nearby houses should be sprayed with an insecticide, and family and other contacts should be immediately immunized. Possible sites where the patient acquired the infection and possible contacts should be investigated. In outbreaks, mass vaccination and vector control must be initiated immediately.[140] A case definition and case finding and confirmatory methods must be established, including clinical facility visits and house-to-house surveys. Mass vaccination during the early phase of an outbreak is difficult because of the delay in recognition of the epidemic and the 5- to 7-day lag between vaccination and appearance of antibody.[148]

Quarantine

Entomologic investigation of an epidemic is necessary to identify the vector, mode of contact with

humans, breeding sites, and methods of control. *Aedes* mosquito breeding places must be eliminated. No quarantine is required for individual cases, but quarantine measures apply to all transportation coming into and out of affected areas. WHO International Health Regulations state that every port and airport be kept free of *A aegypti* in an area extending 400 m outside the perimeter of the facility.[158] Specimens must be sent to reference laboratory testing facilities, and once yellow fever is confirmed, testing should be established in a local facility or even in the field.

The International Health Regulations of 1969 mandate the reporting of yellow fever cases to WHO and neighboring countries. Travelers coming from "infected local areas" into "yellow fever receptive areas" may be required to possess a valid international certificate of vaccination or spend 6 days in quarantine.[62p553–558] This vaccination certificate is valid for 10 years, starting 10 days after the vaccination date. Exposure should be avoided until 5 days after vaccination.

Vaccine. In 1928 in Dakar, West Africa (now Senegal), Mathais infected rhesus monkeys with the blood from a yellow fever patient. This yellow fever virus, which became known as the "French strain,"[159] was used to infect mouse brains and so to produce the first effective yellow fever vaccine. It was named the French Neurotropic Vaccine (FNV). It was used for mass immunization in French West Africa from the early 1940s until 1965 and nearly eliminated yellow fever there. However, encephalitis occurred in some children who received the vaccine. One investigator reported 3 cases per 1,000 vaccinees, with a fatality rate of 38%.[154] Routine use of the vaccine in children in West Africa was stopped in 1961.

In 1937, Thieler at the Rockefeller Institute developed an attenuated live virus vaccine, strain 17D, which led to the substrains (17D-204 and 17DD) used for current vaccines. The 17D strain originated from blood of a 28-year-old West African man named Asibi who had mild yellow fever.[137] The original Asibi strain was passed many times in mouse embryonic cell culture, eventually producing an attenuated mutant. The attenuated strain was designated 17D and in 1937 was used for human immunization. The US Army approved use of the 17D vaccine on 30 January 1941. From February to December 1942, however, 49,111 cases of hepatitis, with 81 deaths, were caused by the 0.04 mL of human serum in each dose of vaccine.[160] A serum-free vaccine was formulated, and no further hepatitis cases occurred.

The 17D strain yellow fever vaccine is one of the safest and most effective live, attenuated vaccines. The vaccine induces an antibody response in more than 95% of vaccinees within 10 days, and neutralizing antibodies persist 30 to 35 years after vaccination. Since 1965, more than 250 million doses of 17D vaccine have been administered.[161] Less than 5% of vaccinees develop mild headache or fever. Encephalitis has been noted in 20 recipients, 14 of whom were under 6 months old. One recipient died, but the encephalitis resolved without sequelae in the other cases. As a result, the vaccine is contraindicated in children under 4 months of age, and children between 4 and 9 months should be vaccinated only when the risk of yellow fever exposure warrants it. Preventive immunization is extremely effective, but the program must continue to immunize individuals born or immigrating into the population. Currently, 17 African countries use routine yellow fever immunization, most in infants at 9 months of age.[62] This approach is recommended by the WHO in yellow fever–endemic countries.

Vaccination during pregnancy has been relatively contraindicated because of the theoretical risk of transplacental infection and postvaccinal encephalitis in the fetus.[155] During an epidemic, however, the maternal risk from natural infection is much greater than the risk from the vaccine. Only one study on the use of the vaccine by pregnant women has been reported, and no effect on the fetus was found.[162] However, one case has been reported of congenital yellow fever infection without malformation in the child; the woman was immunized during pregnancy.[163] The vaccine is not recommended when live-virus vaccines are contraindicated, such as in immunodeficient individuals or those on immunosuppressive drugs. The vaccine is recommended for asymptomatic individuals who are seropositive for human immunodeficiency virus; the risk in symptomatic seropositive individuals is unknown.[62]

Factors that may decrease the efficacy of the vaccine include poor nutritional status, simultaneous administration of the cholera vaccine, and pregnancy. Cholera vaccine given with or up to 3 weeks before yellow fever vaccine causes a temporary reduction in antibody response. In pregnant women, seroconversion rates were found to be only 39%.[162] Prior yellow fever vaccination or concomitant administration of other vaccines, such as those for tuberculosis (bacille Calmette-Guérin [BCG]), diphtheria, pertussis, tetanus, measles, polio, hepatitis A, hepatitis B, and typhoid fever (injectable), or immunoglobulin does not interfere with the antibody response to the vaccine.[164–166] At usual antimalarial doses, chloroquine does not decrease the immune

response.[167] Presence of antibodies against other group B arboviruses does not interfere with the immunogenicity of yellow fever vaccine. Presence of antibodies against other group B arboviruses, including Japanese encephalitis virus, does not interfere with the immunogenicity of yellow fever vaccine.[168] The vaccine must be handled carefully under field conditions.[140] A cold chain must be maintained, keeping the vaccine frozen or at 4°C. Reconstituted vaccine should be used within 1 hour and any residual discarded.

Allergic reactions to the vaccine occur rarely (1 in 1 million recipients) and primarily in persons with an allergy to eggs.[141] One patient with a history of egg allergy was skin tested with a skin prick test of the yellow fever vaccine diluted 1:10 and then an intradermal test of yellow fever vaccine diluted 1:100. There was no reaction, and the yellow fever vaccine was administered without complication.[169]

[Charles F. Longer]

JAPANESE ENCEPHALITIS

Introduction and Military History

Worldwide, Japanese encephalitis (JE) is the most important mosquito-borne viral encephalitis. Within Asia, JE is a major cause of encephalitis, accounting for more than 35,000 cases and 10,000 deaths each year.[170] In Japan, epidemics of "summer encephalitis" were recorded yearly from 1873 until changes were made in agricultural practices and the advent of universal immunization against JE in the 1960s.[171] At the beginning of World War II, the military anticipated possible epidemics among US forces in the Pacific. To address this, the Commission on Neurotropic Virus Diseases of the Board for the Investigation and Control of Influenza and Other Epidemic Diseases in the Army (later reorganized as the Army Epidemiological Board) assigned MAJ Albert Sabin to develop a vaccine against JE and then to stockpile it. Sabin built on earlier work of Japanese investigators[172] to grow Japanese encephalitis virus (JEV) (Nakayama strain) to high concentrations in the brains of sucking mice, make a 10% suspension of the brains, and inactivate the virus with formalin. By 1942, lyophilized vaccine had been produced and shown to be safe in volunteer medical students and laboratory staff in Cincinnati, Ohio. Neutralizing antibodies were elicited in just over 50% of recipients.[173] In July 1945, an epidemic of summer encephalitis occurred among the native and US military populations of Okinawa and nearby islands. Within 10 days of the first case reports, vaccine was administered to US military personnel in the high-risk areas. As many as 70,000 personnel received two doses of vaccine, which was generally well tolerated. Among the 55,000 for which follow-up data were available, however, there were 19 systemic, immediate-type allergic reactions and four instances of "infectious polyneuritis" (Guillain-Barré syndrome).[174] In 1946, 250,000 military personnel in the Far East received this vaccine and the decision was made to vaccinate all Occupation troops.[172]

Starting in 1946, mouse brain–derived vaccine, which lost its potency during storage, was replaced with a more stable, inactivated vaccine derived from chick embryo.[175] JE vaccine was routinely administered to all US military personnel in the Far East Command between 1946 and 1951 and to tens of thousands of Japanese children, in whom its protective efficacy was estimated to be nearly 80%.[176,177] In 1950 despite the vaccination policy, 299 cases of proven or suspected JE occurred among US soldiers in Korea.[178] In 1952, the Army stopped the routine use of JE vaccines.[179] With the availability of more recent vaccines described below, including a more highly purified version of the mouse brain vaccine, JE has been less of a problem for military units in endemic areas, although there were cases among US and Australian troops during the Vietnam War[180,181] and more recently among military personnel stationed in Okinawa.[182] JEV remains a threat throughout Asia.

Description of the Pathogen

JEV was first isolated in Japan in 1935 from the brain of a patient dying from summer encephalitis.[183] This "Japanese" encephalitis was also called type B encephalitis to differentiate it from the type A encephalitis (von Economo encephalitis or encephalitis lethargica), which occurred during winter months and had a different clinical course. Encephalitis epidemics in 1933 and 1937 in the United States were initially thought to be caused by the same virus (type B). Cross-challenge and cross-neutralization studies in mice demonstrated that the St. Louis type B encephalitis virus was distinct from the Japanese type B encephalitis virus.[184] The designation "type B" is no longer used.

JEV belongs to the virus family *Flaviviridae* and genus *Flavivirus*.[185] It is a small, enveloped, positive-stranded RNA virus, 40 to 50 nm in diameter. The genome is approximately 11 kilobases in length, coding for a single open reading frame that trans-

lates into three structural proteins (C, M, E) and seven nonstructural proteins (NS1, NS2a, NS2b, NS3, NS4a, NS4b, NS5).[186,187] There is only one serotype of JEV, although two immunotypes of JEV (Nakayama and JaGAr) have been suggested.[188] Several genotypes have been identified (those having more than 12% divergence), but associations between virus genotypes and disease severity remain uncertain.[189]

Epidemiology

Transmission

The principle vector for JEV in Asia is the *Culex tritaeniorhynchus* mosquito, which is zoophilic.[190] Humans are considered to be a dead-end host for this virus because of the preference of vector mosquitoes for animals over humans.[191] Also, virus is only rarely isolated from blood in patients, suggesting that the duration and titer of viremia may be too low to support transmission. Pigs and birds are the most important animals for virus maintenance, amplification, and spread. Most mosquitoes and animals infected with JEV remain well, but fatal encephalitis occurs in horses and fetal wastage may occur in infected sows.[170] Animal vaccines for pigs and horses are available.[192,193]

While *C tritaeniorhynchus* is the principle vector, many other species of mosquitoes have been infected with JEV in the laboratory and have been found infected in field collections; this suggests that they serve as vectors to a certain degree.[194] In most endemic regions, *C tritaeniorhynchus* mosquitoes are present in large numbers following seasonal periods of heavy rain. This mosquito breeds in swamps, marshes, and rice fields away from human housing but can fly up to a kilometer and a half and has been found in tree tops 15 m (50 ft) off the ground seeking blood meals.[190,195] The mosquito is most active during the hour following sunset.[196]

Geographic Distribution and Incidence

Countries or areas that have had proven epidemics of JE are Australia (Torres Strait[197]), Bangladesh, Burma, Cambodia, China, India, Indonesia, Japan, the Korean peninsula, Laos, Malaysia, Nepal, Philippines, Saipan, maritime Siberia, Singapore, Sri Lanka, Thailand, and Vietnam[194,198](Figure 35-12). A single case diagnosed by polymerase chain reaction (PCR) has been reported from Pakistan.[199] Epidemiologic data are limited because most countries report only total numbers of encephalitis without more specific diagnoses.

In endemic areas, the highest age-specific attack rates occur in children 3 to 6 years of age. Fewer cases in younger children may be due to protection from maternal antibody in the first year and avoidance of vector mosquitoes. With increasing age, children tend to play more outside, especially after dusk, which increases exposure.[200] In some areas (eg, Nepal, northern India, Sri Lanka), all age groups are affected, suggesting recent introduction of the virus into these relatively nonimmune populations.[201] Adult travelers to endemic areas are susceptible to JEV infections.[198]

JEV transmission in the tropics may occur year round. Seasonal epidemics generally begin during the rainy seasons, when mosquito populations are maximal.[201] JEV transmission is not static and may increase due to the construction of dams, use of irrigation, and changes in pig-raising practices and similar activities.

Pathogenesis and Clinical Findings

Infection with JEV may be asymptomatic or manifest as a mild febrile illness, aseptic meningitis, or classic severe meningomyeloencephalitis.

Asymptomatic Infection

Between 25 and 300 JEV infections occur for each identified clinical case of JE.[202–205] Why some infections progress and others remain subclinical is not clear. Viral factors may be important, such as route of inoculation, virus titer in mosquito saliva, and

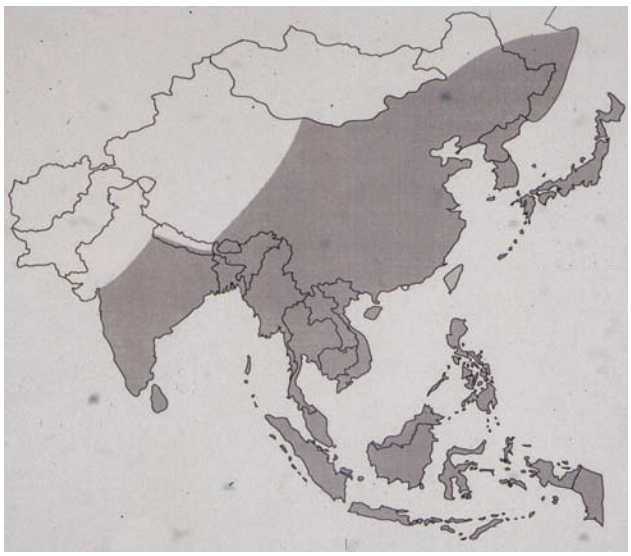

Fig. 35-12. Geographical distribution of confirmed or suspected cases of Japanese encephalitis.

neurovirulence of the inoculum. Host factors, such as age, genetic makeup, general health, and preexisting immunity, may play a key role in disease severity. Virus inoculated directly into a blood vessel by the infecting mosquito may be transported more rapidly to the central nervous system; virus inoculated subcutaneously may proliferate harmlessly for several life cycles of the organism before entering the circulatory system, allowing time for an immune response.[194]

Encephalitis

Following an incubation period of 1 to 2 weeks, patients typically present following 1 to 3 days of fever and headache, often accompanied by nausea or vomiting; they may also be stuporous or comatose. Generalized seizures are common, especially in children. Physical findings include fever, a depressed state of consciousness, and impairment of cranial and motor nerves. Stupor progresses to coma that, in nonfatal cases, may resolve in 1 to 2 weeks. A severely depressed sensorium at the time of presentation is associated with a poor outcome.[206] The mortality rate is approximately 25%; 50% suffer neuropsychiatric sequelae and 25% recover fully.[200,207] Comatose patients may experience respiratory arrest and require ventilatory support. A mild-to-moderate viral pneumonitis is common and may be followed by bacterial pneumonia. Computer tomography and magnetic resonance imaging reveal typical acute and convalescent changes that involve the thalamus, basal ganglia, and other areas.[208–211] Long-term sequelae in survivors include weakness, ataxia, tremor, athetoid movements, paralysis, memory loss, and abnormal emotional behavior.[212,213]

Autopsy of fatal cases has shown the brain to have vascular congestion, mild edema, and minimal overlying cellular exudate.[214] Virus can be isolated from all areas of the brain, but virus is most commonly found in the thalamus and brain stem. The destruction of neurons in the brain stem can explain the profound coma and respiratory failure.[215]

Diagnostic Approaches

An acute febrile illness with changes in mental status and signs of meningeal irritation occurring in endemic areas for JE should prompt the physician to consider JE as the cause. In some areas where diagnostic support is limited, a presumptive diagnosis of JE is made if the cerebrospinal fluid (CSF) is clear. Other conditions that should be considered are shown in Table 35-6.

CSF findings that are consistent with a diagnosis of JE include an opening pressure for the CSF that is normal or moderately increased, a total protein that is slightly increased, and a lymphocyte pleocytosis that is typically 10 to 1,000 mononuclear cells per milliliter.[200] The presence of JEV-specific immunoglobulin M (IgM) in the CSF is thought to be diagnostic of JE, as opposed to infection with JEV without encephalitis which results in increased IgM in the sera but not in the CSF.[216] The presence of infectious virus in the CSF and low levels of JEV-specific IgM in both CSF and serum at presentation are associated with a poor outcome.[206]

Many methods of detecting JEV antibodies have been developed. The most reliable method at present is a carefully standardized enzyme-linked immunosorbent assay (EIA). This approach distinguishes between JE and dengue infections, as well as primary and secondary flavivirus infections, by comparing the number of units of specific IgM versus immunoglobulin G antibody.[217] Hemagglutination inhibition is a simple and reliable approach,[218] but its interpretation may be more difficult than the EIA's. Antibody test results may be confusing because of considerable cross-reactivity with other flaviviruses.[219] In Southeast Asia, where dengue and JEV both circulate, previous exposure to either virus in an individual patient increases the difficulty of virus-specific serological diagnosis. Natural infection or vaccination for yellow fever, West Nile fever, or tick-borne encephalitis may also produce false-positive tests for JEV antibody.

The PCR can be used to detect viral genome.[220] Isolation of JEV may be performed in mosquito or other cell lines. Virus isolation from brain tissue gathered postmortem is usual, but positive cultures from CSF are much less common, and isolations from serum are rare.[221] Because of the low sensitivity of viral detection methods, diagnosis is usually based on the presence of JEV-specific IgM antibodies in the CSF or serum. Commercial assays are just becoming available, although none are currently licensed in the United States. Specimen testing can be coordinated through the Armed Forces Research Institute of Medical Sciences in Bangkok, Thailand; the Centers for Disease Control and Prevention in Fort Collins, Colorado; or the Walter Reed Army Institute of Research in Silver Spring, Md.

Recommendations for Therapy and Control

Therapy

Currently, there is no effective treatment for JE beyond supportive care. Dexamethasone does not reduce mortality nor provide any other benefit but

TABLE 35-6

DIFFERENTIAL DIAGNOSIS OF FEVER AND MENINGISMUS OR ALTERED MENTAL STATE IN AREAS WHERE JAPANESE ENCEPHALITIS IS ENDEMIC

Diagnosis	Specific Therapy Available
Disease states lacking a CSF pleocytosis	
-Metabolic encephalopathy complicating infection or other systemic process	Yes
-Cerebral malaria	Yes
-Dengue encephalopathy	No
-Acute toxic encephalopathy including Reye's syndrome	No
-Sub-arachnoid hemorrhage	No
Disease states with CSF pleocytosis and low CSF glucose	
-Pyogenic meningitis	Yes
-Tuberculous or fungal (cryptococcal) meningitis	Yes
Disease states with CSF pleocytosis and normal glucose	
-Brain abscess	Yes
-Infections associated with immunosuppression: toxoplasmosis, progressive multifocal leukoencephalopathy, etc.	Yes (for some)
-Aseptic meningitis	
Leptospirosis	Yes
Rickettsioses	Yes
-Cerebral vasculitis	Yes
-Acute viral encephalitis	
Herpes simplex encephalitis	Yes
Japanese encephalitis	No
West Nile encephalitis (overlap with JE in western India)	No
Murray Valley encephalitis (overlap with JE at southern limit of JE virus range)	No
Meningoencephalitis due to enteroviruses (eg, Coxsackie, echo, polio viruses)	No
Rabies	No
Encephalitis due to viruses of the California encephalitis virus serogroup (viruses present in Sri Lanka and China by serology; no human cases recognized)	No
-Parainfectious and postvaccinal encephalomyelitis	
Measles encephalitis	No
Varicella-zoster encephalitis	No
Disease following other infections: rubella, mumps, infectious mononucleosis, influenza, parainfluenza, *Mycoplasma* infection	No
Disease following vaccinations: Semple rabies vaccine, measles vaccine	No

CSF: cerebrospinal fluid
JE: Japanese encephalitis
Adapted from: Innis, BL. Japanese encephalitis. In: Porterfield, JS, ed. *Kass Handbook of Infectious Diseases: Exotic Viral Infections*. London: Chapman & Hall Medical, 1995. Reproduced with permission of Edward Arnold Limited.

is still sometimes used despite the lack of evidence of efficacy.[200] Various interferons have shown promise, but definitive trials have not been done.[222,223]

Approaches to the prevention of JE include vector control, vector avoidance, immunization of susceptible persons, and immunization of amplifying hosts.

Vector Control and Personal Protection

Spraying pesticides produces limited reductions of JEV vectors in a limited area for a limited amount of time at great cost. Reasons for this lack of effectiveness include: (*a*) the vector *C tritaeniorhynchus* has a wide flight range, so new mosquitoes quickly replace those killed by local spraying of insecticides in and around human and animal housing areas; (*b*) application of insecticides to rice fields to kill larvae is effective for only 1 to 2 weeks; and (*c*) organophosphorus and carbamate insecticides have become largely ineffective because of the development of insecticide resistance.[224]

Personal precautions should be taken by residents of endemic regions and travelers to these areas to avoid mosquito bites. These precautions include:

- minimizing outdoor exposure at dusk and dawn and on overcast days,
- sleeping in screened quarters or under mosquito netting,
- wearing clothing leaving a minimum of skin bare,
- using insect repellents containing DEET (N,N-diethylmeta-toluamide) appropriately on exposed skin surfaces,[225] and
- keeping farm animals away from housing and avoiding the animals at dusk.[226]

Vaccination

Vaccines that are distributed commercially contain formalin-inactivated virus derived from mouse brain. This type of vaccine was first tested in humans in Japan and Russia in the late 1930s and licensed in Japan in 1954. Partial purification with protamine sulfate was introduced in 1958. The presently available vaccine—JE-VAX, produced by BIKEN (The Research Foundation for Microbial Disease of Osaka University, Japan) and distributed in the United States since 1992 by Pasteur-Adventist, USA—is more highly purified.[227]

Efficacy and Safety. Vaccine efficacy trials have been reviewed,[194,198,227] and efficacy has ranged from 81% to 96%. Among pediatric participants, fever has followed immunization in less than 1% of the vaccinees and local reactions have been seen in approximately 5%. The most definitive trial was performed in Thailand from 1984 to 1985.[228] The highly purified BIKEN vaccine (Nakayama-Yoken strain) and a bivalent vaccine consisting of Nakayama-Yoken and Beijing-1 strains were compared in a placebo-controlled, masked, randomized study. Two doses of vaccine, given a week apart, were administered to approximately 22,000 children in each of the three groups. The efficacy of both monovalent and bivalent vaccines was 91%. There were no major side effects. Minor side effects, such as headache, sore arm, rash, and swelling, were similar to the control group (who received tetanus toxoid) and generally affected less than 1%.

JE vaccine safety and immunogenicity trials began in the United States in 1983. One hundred twenty-six volunteers received two 1.0 mL doses of the vaccine 1 week apart. A three-dose series was recommended after two doses failed to provide an optimal immune response. Adverse reactions included one apparent immediate hypersensitivity reaction to the first dose, manifested by generalized urticaria that responded to subcutaneous epinephrine. Eighteen percent reported tenderness at the injection site, and 9% reported headache lasting an average of 1 day.[229]

In expanded US trials from 1987 to 1989, 4,034 US military volunteers received vaccine without severe adverse reactions. Twenty percent of the volunteers reported mild arm soreness lasting no more than a few hours; 10% reported headache. These studies also suggested the need for a third dose,[230] and subsequent studies have demonstrated that the antibodies produced by a three-dose primary series of JE-VAX persists for at least 3 years in healthy US soldiers.[231]

Although the safety record of JE vaccines used in Japan has been excellent, reports from Denmark, Australia, and Canada in the 1990s have suggested an increased incidence of hypersensitivity reactions.[232–234] In a prospective study of US military personnel and their family members on Okinawa, the hospitalization rate for treatment of refractory urticaria following vaccination was 3 per 10,000. A history of urticaria increased the risk of an adverse reaction 9-fold.[227] Nevertheless, the vaccine is generally felt to be safe for individuals at risk for the disease.[235,236] Due to the risk of hypersensitivity reactions, it is recommended that persons receive the vaccine at least 10 days before departure to assure their access to medical care should the need arise.

Indications for Vaccination. Current recommendations from the Advisory Committee on Immunization Practices (ACIP) for primary and booster vaccination are given in Table 35-7. A three-dose vaccination series is recommended for US inhabitants traveling to areas where they may be at risk of exposure to JEV. Most travelers to Asia will not require JE vaccination. JEV transmission is seasonal and confined to rural areas where animals are present. Consulting with public health officials before travel may clarify the need for immunization. Living for extended periods in endemic areas and

TABLE 35-7

RECOMMENDED SUBCUTANEOUS IMMUNIZATION SCHEDULE FOR BIKEN JAPANESE ENCEPHALITIS VACCINE

	< 3 y of age	≥ 3 y of age	Schedule
Primary series	0.5 mL	1.0 mL	0, 7, and 30 d*
Booster	0.5 mL	1.0 mL	Dose at 2 y and then at 3-y intervals or as determined by serology

* The primary series may be given at 0, 7, and 14 days, but this will result in lower neutralizing antibody titers.

Source: Advisory Committee on Immunization Practices. Inactivated Japanese encephalitis virus vaccine: Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR.* 1993;42(RR-1):1–15.

having contact with farm animals, especially in the evening, will increase risk. Vaccination is not indicated for travel to urban centers in Asia for short periods. JE incidence figures for the area to be visited may not be helpful if the vaccine is in widespread use. The vaccine may be given with the diphtheria-tetanus-pertussis, measles, and oral polio vaccines, but its interaction with other vaccines is unknown.[198] In addition to selected military units and individuals traveling to high-risk areas, vaccination is recommended for those participating in Cobra Gold exercises in Thailand and for units on alert status for possible missions into JE-endemic areas. Updated country information is available from the resources listed in Chapter 11, Medical Threat Assessment.

Contraindications. Contraindications to immunization are as follows. Persons with a history of significant reaction to JE vaccine should not receive additional doses. Although no adverse outcomes have been associated with administration during pregnancy, it should be avoided unless significant exposure to JEV cannot be otherwise avoided. There are no safety data for children younger than 1 year of age. As mentioned above, persons with a history of allergic conditions, such as asthma, allergic rhinitis, drug or hymenoptera venom sensitivity, food allergy, and especially urticaria, seem to be at increased risk. These persons should be advised of the potential for vaccine-related angioedema and generalized urticaria.

[David W. Vaughn]

THE EQUINE ENCEPHALITIDES

Introduction and Military Relevance

Venezuelan, western, and eastern equine encephalitis viruses have been recognized as causative agents of fatal neurologic disease in horses since the first half of the 20th century. By the 1930s, advances in the field of virology had made isolation and basic characterization of these disease-causing agents possible. Western equine encephalitis (WEE) virus was first isolated from sick horses in 1930.[237] Eastern equine encephalitis (EEE) virus and Venezuelan equine encephalitis (VEE) virus were similarly isolated and described by the end of the 1930s.[238–240] While these viruses were initially described during the first half of the 20th century, their presence in the Americas almost certainly predates the arrival of the Spanish in the New World. There are anecdotal stories of Spanish invaders entering Colombia with thousands of horses and leaving with only a few surviving animals. While not necessarily attributable to the equine encephalitides, such mortality testifies to the presence of severe horse disease in that area during the early 16th century. First recognized as horse diseases, the equine encephalitides became associated with naturally occurring cases of encephalitis in humans by the late 1930s,[241,242] and the importance of this group of viruses in the Americas was firmly established.

Because of their endemnicity throughout Central and South America, the equine encephalitides are significant health threats to US troops deployed in these areas. The risk is significant enough that preventive vaccination has been requested for service members participating in special missions in these areas. Cases of VEE have been reported in troops conducting training exercises in Central America.[243,244]

While VEE, WEE, and EEE viruses were recognized as the etiologic agents of encephalitis in horses and humans in the 1930s, it was not until EEE virus was isolated from *Culiseta melanura*[245] mosquitoes in the 1950s that there was some indication that these viruses were transmitted by mosquitoes. Today these viruses are collectively grouped, along with several Old World mosquito-borne viruses, into the genus *Alphavirus* (formerly known as the group A arboviruses) in the family *Togaviridae*.

Description of the Pathogen

While the names given to the equine encephalitis viruses—VEE, WEE, and EEE viruses—suggest that these are individual agents, each represents a complex of serologically related viruses that, together with four additional virus complexes, have been grouped together into the *Alphavirus* genus.[246]

The alphaviruses are spherical particles, typically 60 to 65 nm in diameter. Alphavirus particles are composed of a lipid envelope containing two structural glycoproteins (El and E2) surrounding a protein core. The icosahedral protein core or nucleocapsid contains the viral ribonucleic acid and forms the backbone for the overall shape and structure of the mature virion.[247] The envelope glycoproteins form heterodimers that further associate to form trimers.[248,249] It is these trimers, which form the spikes, that are clearly visible on electron micrographs of alphavirus particles[250] (Figure 35-13). Alphavirus spikes are the major targets of the host's immune response to infection[251] and directly influence important biological characteristics of this group of viruses, such as tissue tropism, host range, and virulence.[252]

Alphavirus replication involves the classic steps of viral replication, including viral attachment, uncoating, transcription, translation, packaging, and escape and has been reviewed in detail.[247]

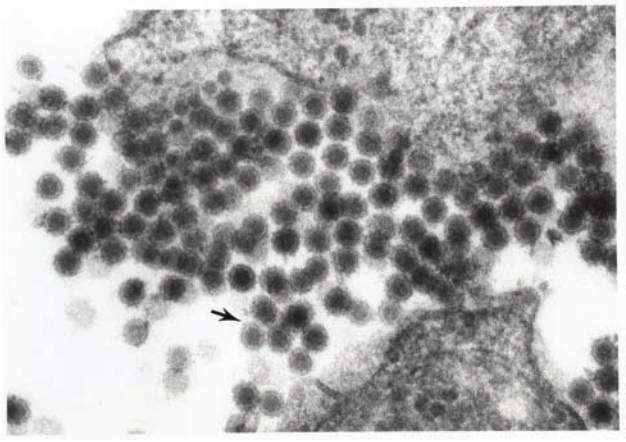

Fig. 35-13. An electron micrograph of Vero cells infected eastern equine encephalitis virus (140,000x magnification). The arrow identifies the viral envelope, which contain heterodimer spikes composed of glycoproteins E1 and E2.
Photograph courtesy of Tom Geisbert, Pathology Division, US Army Medical Research Institute of Infectious Diseases.

TABLE 35-8

CLASSIFICATION OF THE VENEZUELAN EQUINE ENCEPHALITIS VIRUS ANTIGENIC COMPLEX

Subtype	Variety	Epidemiology
I	A/B	Epidemic/epizootic
I	C	Epidemic/epizootic
I	D	Endemic/enzootic
I	E	Endemic/enzootic
I	F	Endemic/enzootic
II	Everglades	Endemic/enzootic
III	A (Mucambo)	Endemic/enzootic
III	B (Tonate)	Endemic/enzootic
III	C (71D-1252)	Endemic/enzootic
IV	Pixuna	Endemic/enzootic
V	Cabassou	Endemic/enzootic
VI	AG80–663	Endemic/enzootic

Epidemiology

The VEE complex consists of six closely related subtypes, each differing in its ecology, epidemiology, and virulence for humans and equines. The IA/B and IC varieties are commonly referred to as epizootic strains (Table 35-8). These strains have been responsible for extensive epidemics in North and South America and are highly pathogenic for both humans and equines.[246] All of the epizootic strains are exotic to the United States and have been the etiologic agent responsible for natural epidemics only twice since 1973.[253] An outbreak of fatal encephalitis caused by epizootic VEE virus between April and October of 1995 in Venezuela and Colombia was the first major outbreak since the 1970s.[254]

The WEE virus complex consists of six viruses: WEE, Sindbis (SIN), Y 6233, Aura, Fort Morgan, and Highlands J. The EEE virus complex consists of a single virus found in two antigenically distinct variants, the North and South American forms. All North American and Caribbean isolates show a high degree of genetic and antigenic homogeneity, whereas South and Central American isolates tend to be much more heterogeneous.[255,256]

Transmission

Understanding the epidemiology of the equine encephalitides in humans requires an appreciation of the factors affecting the mosquito vectors and vertebrate hosts and their interactions in naturally occur-

ring endemic foci. Most commonly, disease in humans follows expansion or intrusion into geographic regions and ecological zones where natural transmission cycles are in progress. Human activities that disrupt or alter natural transmission cycles, such as introduction of alien mosquito vectors or unnatural modifications to the environment, may predispose human populations to disease. Natural changes to the environment or alteration of the viruses themselves through accumulation of genetic mutations may also be contributing factors to human disease.

The epizootic subtypes of VEE virus are more opportunistic, relying on a variety of mosquito species and any susceptible equines that may be present (Figure 35-14). Horses, donkeys, and mules serve as important amplifying hosts because they develop high-titer viremias capable of infecting many mosquito species. Varieties D, E, and F of subtype I and subtypes II, III, IV, V, and VI are referred to as the enzootic strains (see Table 35-8).[246,254] Like the epizootic strains, the enzootic strains may cause disease in humans, but they differ from the epizootic strains in their lack of virulence for horses. Infection of horses with enzootic subtypes leads to an immune response capable of protecting animals from challenge with epizootic strains.[257] Limited data, acquired after accidental laboratory exposures, suggest that similar cross-protection may not occur in humans.[258,259]

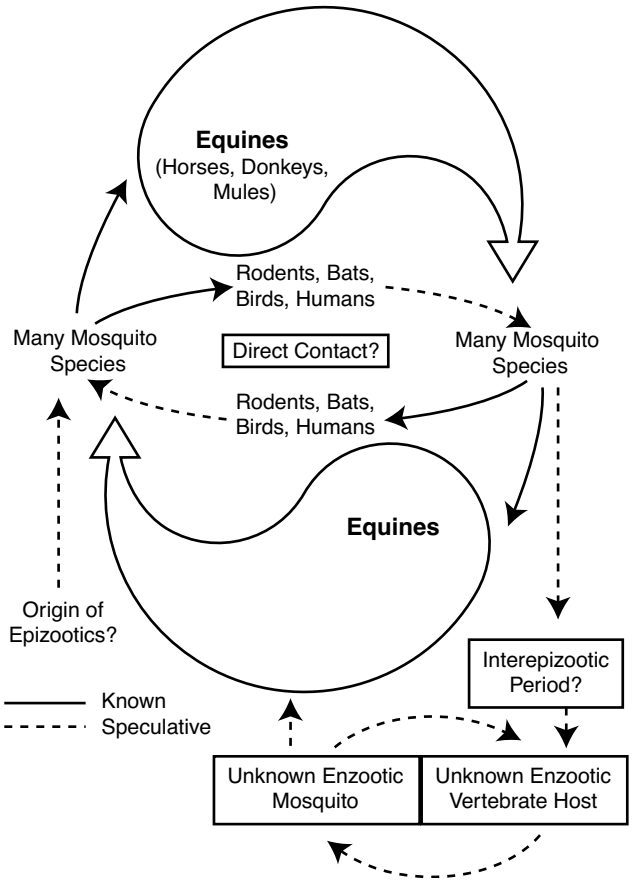

Fig. 35-14. Transmission cycle of epizootic and enzootic subtypes of Venezuelan equine encephalitis virus. Horses, donkeys, and mules are the principle amplifying hosts for the epizootic subtype of the virus, and mosquitoes from at least four genera have been implicated in transmission. For the enzootic subtype, *Culex (Melanoconion) taeniopus, C aikenii,* and *C portesi* are species that have been implicated as important vectors in past outbreaks. Art by Annabelle Wright, Walter Reed Army Institute of Research.

Enzootic VEE virus subtypes are maintained quite efficiently in transmission cycles involving mainly mosquitoes belonging to the subgenus *Melanoconion*. The mosquitoes are ground feeders and prefer feeding on mammals rather than birds.[260] In part because their ecology is similar to that of the mosquito vector, ground-dwelling rodents serve as the primary vertebrate host for the enzootic forms of VEE virus. After infection, these animals develop viremias of sufficient magnitude and duration to infect mosquitoes during their blood meals.[261] Other animals, such as bats and certain birds, may play a secondary role.[258,259]

Unlike the enzootic strains, the fate of the epidemic strains during interepidemic periods is unclear. As epidemic forms of VEE virus appear so rarely, the natural ecology of these viruses has been difficult to study. The two most likely theories suggest that either epidemic strains evolve from enzootic strains[264,265] or they are maintained in cryptic foci, remaining undetected for long periods of time.

WEE virus is maintained in transmission cycles involving perching birds and the mosquito *Culex tarsalis.* Humans and horses become involved only tangentially and are considered dead-end hosts.[266] Endemic and epidemic WEE virus activity in California has been extensively studied.[267] Results from these studies suggest that enzootic activity is difficult to control completely.

Enzootic transmission of EEE virus occurs almost exclusively between perching birds and the mosquito *Culiseta melanura*.[268,269] Because of the strict ornithophilic feeding behavior of this mosquito, human and equine disease requires the involvement of more general feeders, such as members of the genera *Aedes* and *Coquillettidia*.[257] Equines are typically dead-end hosts for EEE virus. They may, however, develop viremias of sufficient magnitude following infection to infect vector mosquitoes, but this is not considered an important mechanism of virus dissemination.[253]

In the case of naturally occurring outbreaks of VEE, WEE, and EEE, evidence of infection in equines almost always precedes human disease.[270,271] With EEE and WEE viruses, isolations are also often made from domestic or wild birds before the onset of human involvement, making these hosts useful for detecting potential epidemic activity.[272] With VEE, the magnitude of viremias in infected horses can be extremely high; as a result, these animals can serve as efficient amplifying hosts.

Geographical Distribution

Most subtypes of VEE viruses are enzootic in South and Central America, but subtype II circulates in the Everglades region of Florida. The enzootic viruses are commonly isolated in specific ecological habitats, where they circulate in transmission cycles primarily involving rodents and *Culex* mosquitoes of the *Melanoconion* subgenus.[273–275] These mosquitoes often occur in very humid localities with abundant open spaces, such as sunny, swampy pastures cut by slowly flowing, meandering streams. EEE virus is endemic to focal habitats ranging from southern Canada to northern South America.[253] The virus has been isolated as far west as Minnesota but is most common along the eastern coast of the United States between New England and Florida. Several antigenic subtypes of WEE virus have been identified, but the geographic distributions of the subtypes overlap.[15] Most members of the WEE virus complex are distributed throughout the Americas, but the SIN virus and Y 62–33 subtypes are found only in the Old World.[246]

The largest known outbreak of epidemic VEE occurred in the late 1960s and early 1970s. Epidemic virus first reached Mexico in 1966 and eventually reached the United States in 1971. A study of this virus in Central America, Mexico, and the United States showed that the virus easily invaded territories in which it was formerly unknown.[276] This probably resulted from the availability of large numbers of susceptible equine hosts and the presence of competent mosquito vectors. Immunization of millions of horses throughout North America and unprecedented mosquito abatement efforts eventually stopped the epidemic before it was able to spread north of Texas.[277,278] Epidemic VEE virus has not been isolated in the United States since the 1971 outbreak.

An outbreak of the epidemic IC strain of VEE virus between April and October 1995 occurred in Colombia and Venezuela and involved 75,000 to 100,000 people.[254] Factors contributing to this outbreak included greater than normal rainfall resulting in large increases in vector populations, decreased surveillance for the virus, and accumulation of large numbers of susceptible horses as a result of reduction or elimination of vaccination programs. The epidemiology of disease in humans was typified by its sudden appearance, rapid increase, and brief occurrence in affected communities. In hospitals in Manaure and Riohacha in northern Colombia, admissions of cases consistent with VEE reached 330 per day. Interestingly, 90% of the cases were seen within 2 weeks in September and October.[279]

Incidence

While VEE virus has been quite active in recent years, the median number of cases of EEE and WEE during the same time period in the United States has been less than 5 each annually.[280] In the United States, EEE activity peaks between July and October in the northern part of its range and between May and August in the southern part. Human cases of EEE in Florida have occurred year-round.[281] Humans living in or near endemic foci for VEE have a high seroprevalence rate, often 100%, reflecting their cumulative experience with continuous transmission that occurs in these areas.[246] Epidemic transmission of VEE virus is sporadic, occurring only twice during the last 30 years. During both epidemics, thousands of individuals were involved, resulting in many deaths.[276]

VEE has been a problem in US service members deploying to endemic areas. On at least two occasions, soldiers undergoing jungle operations training in Fort Sherman, Panama, became ill with fever, chills, and headache.[243,244] On both occasions, infections occurred during the last quarter of the year, a time in Panama characterized by increased vector populations brought on by heavy rainfall. While Panama has been the source of all known VEE virus exposures in US soldiers, deployment to any VEE virus–endemic area within South or Central America presents significant risk to military personnel operating where active transmission is occurring.

Pathogenesis and Clinical Findings

Because outbreaks of viral equine encephalitis occur so infrequently and the majority of human cases occur in rural areas of developing countries, detailed studies on the pathogenesis of the viruses that cause these diseases in humans have not been

completed. From the information that is available, experimentally infected animals serve as adequate models for pathogenesis of fatal encephalitis in humans. However, systemic disease is highly host specific and is dependent on a variety of other factors, including age, immune status, route of infection, and strain and dose of virus. The lymphoid and central nervous systems appear to be common targets in both experimental animal models and humans.[282–286] The Trinidad donkey (TrD) strain of VEE virus causes moderate but reversible lesions to the lymphoid organs in mice and nonhuman primates but causes marked destruction of those organs in guinea pigs and hamsters.[283,284]

Pathological changes to the central nervous system differ significantly depending on the animal models and the strains of virus tested. Inoculating mice with the TrD strain of VEE virus results in diffuse encephalomyelitis,[283,284] while monkeys develop only mild pathological changes to the thalamus, hypothalamus, and olfactory areas of the brain.[284] However, infection of monkeys by the aerosol route, a common route of accidental exposure in humans, can result in much more severe pathology, including perivascular cuffing and nodular and diffuse gliosis, especially in the cortex and hypothalamus.[287] Aerosol exposure of monkeys to a highly pathogenic strain of VEE virus resulted in significant mortality (35%) and development of severe clinical and pathological changes in all animals.[288] Observations on the severity of aerosol infection of nonhuman primates suggest that encephalitis in humans could be a more common occurrence when infection occurs by this route. Aerosol infection is most likely to occur in a laboratory setting, so technicians attempting to isolate and identify the virus are at greatest risk of aerosol infection.

Clinical disease in humans caused by the equine encephalitides falls into one of two general categories. A systemic febrile illness with occasional encephalitis is observed with viruses in the VEE complex, while a primarily encephalopathic syndrome is observed with EEE and WEE viruses. Disease caused by all three groups of viruses begins in a similar fashion. After a relatively short incubation period (1 to 6 days for VEE, 5 to 10 days for EEE, 5 to 15 days for WEE), patients present with chills, high fever, headache, and malaise. With VEE, these symptoms can be quite severe and may be accompanied by photophobia, sore throat, myalgias, and vomiting.[289] Although the majority of VEE infections are symptomatic, less than 1% of adult cases and 4% of childhood cases progress to encephalitis, and mortality rates are relatively low.[290] While no conclusive clinical studies have been conducted, there are some laboratory data to suggest that congenital VEE may be an important cause of fetal malformations and spontaneous abortion in endemic areas.[291,292] EEE is the most severe of the equine encephalitides, having case fatality rates as high as 50% to 75%.[293,294]

As with the other equine encephalitides, the severity of neurological disease seen with WEE increases with decreasing age. Of children less than 1 year old with WEE, greater than 90% will exhibit focal or generalized seizures.[295] Neurological symptoms caused by all of the viruses may include lethargy, somnolence, or mild confusion with or with or without nuchal rigidity. More severe signs may include seizures, ataxia, paralysis, or coma.[296] With EEE, children frequently exhibit generalized facial or periorbital edema and disturbances of the autonomic nervous system, such as impaired respiratory regulation or excess salivation. Neurological sequelae, such as seizures, spastic paralysis, cranial neuropathies, and mental retardation, can occur in up to 30% of survivors.[294,297] Neurological sequelae from VEE and WEE virus infection can also occur, but their incidence and severity are generally less pronounced than from EEE. The clinical presentation of patients with one of the equine encephalitides does not provide sufficient information to make a specific diagnosis.

Diagnostic Approaches

Because of the large number of alphaviruses associated with disease throughout the world, selecting diagnostic methods should be based on a thorough understanding of the clinical features and epidemiology of these viruses.[298] Serum and other biosamples should be frozen at -70°C and immediately transported to theater-area diagnostic laboratories or medical laboratories in the United States for testing.

Epidemiologically significant diagnosis of the equine encephalitis viruses requires one or more of the following: (*a*) presence of virus-specific IgM in serum, (*b*) at least a 4-fold increase in virus-specific serological response between acute and convalescent serum samples, and (*c*) isolation and identification of the virus.

Serological tests for these viruses include hemagglutination inhibition, immunofluorescence, complement fixation, neutralization, or IgG or IgM enzyme-linked immunosorbent assay (ELISA). Of these tests, the IgM-capture ELISA is probably the most useful, as the presence of virus-specific IgM

in a single serum sample can serve as an indicator of recent infection.[299,300] Identification of virus-specific IgM in the cerebrospinal fluid is an extremely useful method of serodiagnosis, because IgM antibodies do not cross the blood-brain barrier. IgM in cerebrospinal fluid, therefore, implies local antibody synthesis in response to infection of the central nervous system.[299] IgM antibodies to alphaviruses in humans appear to be subtype-specific, so variety typing of VEE or WEE virus infection would not be possible with this technique.[301] Diagnosis by other methods requires testing sequential sera from the same patient taken during different phases of disease. A 4-fold increase in antibody titer between acute and convalescent samples is considered diagnostic. Most serological assays for EEE and VEE viruses tend to be quite specific, but low-level cross-reactivity may be noted between WEE and SIN virus antigens.[298]

Isolation of virus is critical to permit differentiation of viral subtypes within the VEE virus complex. VEE, WEE, and EEE viruses can only be isolated from serum samples taken within the first several days of illness. However, virus may be isolated from throat swabs from individuals infected with VEE virus[302] even after viremias have fallen below detectable levels. Isolation of virus from throat swabs has been used successfully for the identification of VEE virus infections in troops stationed in Panama.[243,244] Isolations can be made in suckling mouse brains or in Vero cell cultures with about equal sensitivity. Isolates can be identified by using a variety of techniques but most commonly by cross-neutralization tests or immunofluorescence. Newer methods of virus identification, including polymerase chain reaction and real-time fluorogenic 5'-nucleases assays, show great promise and are now becoming available outside the research setting.

Recommendations for Therapy and Control

No specific therapy exists for treating the equine encephalitides. Therefore, treatment is aimed at managing specific symptoms. Antipyretics and analgesics will help to relieve the fever, headache, and myalgias. In encephalitic cases, anticonvulsants can be used to control seizures, and intravenous mannitol or corticosteroids may be used to control brain edema.

Control of the equine encephalitides is best accomplished through detailed knowledge of viral activity in deployment areas combined with judicious use of vaccination before deployment into endemic or epidemic areas. The US Army has extensive experience with a live-attenuated vaccine for VEE used as an investigational new drug product in humans; it produces moderate-to-strong virus-specific antibody responses in 80% of recipients. However, this vaccine (TC-83) is reactogenic, causing flu-like symptoms in approximately 20% of recipients. TC-83 should not be administered to pregnant women because of the possibility of teratogenic effects.[303,304] Long-term protection against only subtypes IA/B and IC can be expected. The magnitude or duration of a cross-protective response to heterologous subtypes is unknown.

Formalin-inactivated vaccines for human use exist for VEE, WEE, and EEE viruses. While the inactivated VEE vaccine has been shown to be a strong immunogen, it is currently being used only to boost TC-83 nonresponders. The WEE and EEE vaccines are weakly immunogenic and require multiple injections and regular boosters to develop and maintain protective antibody responses. Because of the problems associated with both the live and killed vaccines, it is doubtful that vaccination of rapidly deploying troops would be possible with any of the currently available vaccines. Like the TC-83 vaccine, these inactivated vaccines are only available as investigational products.

Environmental control of VEE, WEE, and EEE is a viable option under certain conditions. Interruption of secondary transmission cycles involving horses and other secondary vector species is likely to be the most efficient method of preventing or controlling epidemic spread of VEE virus. Because epidemic VEE is amplified by equines, vaccinating these animals with TC-83 has been used effectively to control outbreaks. Similar control of endemic VEE, WEE, and EEE is probably not possible because horses do not serve as major amplifying hosts for the viruses that cause these diseases. Widespread mosquito control through the use of insecticides, biological control, and source reduction is effective during epidemic episodes but is probably ineffective for the control of endemic viruses because of the difficulty in identifying restricted endemic foci. In the absence of vaccination or other environmental control procedures, educational programs that reduce mosquito biting rates and increase use of personal protective measures, such as use of insect repellents, bed nets, appropriate clothing, and window screens, are the most effective means of infection control.

Preventing the equine encephalitides will require prior knowledge of their presence in deployment areas coupled with personal protection and use of insect control measures. Currently available inves-

tigational vaccines can be used effectively if they are administered with sufficient time (1 to 2 weeks) for recipients to recover from sometimes deleterious reactions and for administration of booster immunizations when necessary. Vaccination of service members should be considered when they deploy to endemic or epidemic areas. If operational requirements dictate vaccination, the Director of the Research Area Directorate, Medical, Chemical, and Biological Research Program (RAD 4), Fort Detrick, Maryland, may be contacted for information on how to obtain vaccine. A new, safer, and more effective genetically engineered vaccine for VEE is under development by the US Army and should be available in the future. This new vaccine will resolve many of the problems inherent with TC-83 and may be an effective tool for the control of VEE epidemics.

[George V. Ludwig]

TICK-BORNE ENCEPHALITIS

Introduction and Military Relevance

One of approximately 446 known arboviruses, tick-borne encephalitis (TBE) has a wide geographic distribution. At times, it has been a devastating and socially important epidemic and enzootic disease.[305] The involvement of US military forces in European and Asian regions that are endemic for TBE emphasizes the importance of understanding the disease-specific interactions of host, virus, and vector that result in disease or asymptomatic infection. US military personnel represent an immunologically naive population who may be required to perform in an endemic environment in a manner that maximizes their exposure to the tick vector. The combination of these factors produces the potential for a high rate of morbidity and mortality from TBE. A study[306] of US service members who trained extensively in areas of Central Europe endemic for TBE was conducted in 1985. Although clinical symptoms for TBE had not been recognized in this population, three individuals were seropositive for TBE, for a seroprevalence of 1.5% and an estimated infection rate of 0.9/1,000 person-months of exposure. It should be noted that the risk of TBE is geographically focal, even in areas that are considered endemic, and the rates of infection in this military population may not be widely generalizable.

TBE was not clinically recognized until 1927 when Schneider, in southern Austria, described patients with seasonal encephalitis, which he named "meningitis serosa epidemica." Zilber in 1937 further characterized this disease in eastern Siberia, isolated the virus (Russian spring-summer encephalitis virus, now called the Far Eastern subtype of TBE virus), and suggested that the vector for this virus was the tick *Ixodes persulcatus*. In 1954 the first case of TBE was described in Sweden, and TBE virus was isolated from *I ricinus* ticks (Central European encephalitis virus, now known as European or Western subtype TBE virus).[307] TBE is considered the most important arboviral disease in Central Europe. Cases of TBE have been reported from numerous countries, including Sweden, Finland, Denmark, Norway, France, Greece, the Czech Republic, Slovakia, Hungary, Poland, Romania, Turkey, countries of the former Soviet Union and the former Yugoslavia, and the federal states of Saarland and Rhineland Paltinate in Germany.[308] Other names used for this disease include Central European encephalitis, Russian spring-summer encephalitis, Fruhsommer-meningoenzephalitis (FSME), diphasic meningoencephalitis, biundulant meningoencephalitis, diphasic milk fever, Schneider's disease, Kumlingesjukan, Roslagssjukan, and Ryssjukan.

Description of the Pathogen

TBE viruses are one group of approximately 70 members of the family *Flaviviridae*, genus *Flavivirus* (formerly group B arboviruses of the family *Togaviridae*).[309] Flaviviruses have a positive sense genomic RNA, which is single-stranded and approximately 11 kilobases in length.[310]

The TBE complex is composed of eight major viral subtypes: tick-borne encephalitis Far Eastern subtype, tick-borne encephalitis Western subtype, Kumlinge virus, louping ill virus, Omsk hemorrhagic fever virus, Kyasanur Forest disease virus, Langat virus, and Powassan virus[311–313] (Table 35-9). Studies using hemagglutination-inhibition tests with monoclonal antibodies to TBE virus revealed a close antigenic relationship among all subtypes of the TBE complex except for Powassan virus.[314] Based on hemagglutination-inhibition titers, there is a great deal of antigenic similarity among Far Eastern TBE virus, Western TBE virus, louping-ill virus, and Omsk hemorrhagic fever virus.

Epidemiology

Transmission

TBE infection depends on exposure to the tick vector or ingestion of the virus in contaminated milk or milk products. Peak morbidity occurs between the

TABLE 35-9

SUMMARY OF CLINICALLY IMPORTANT TICK-BORNE ENCEPHALITIS COMPLEX VIRUSES

Far Eastern Tick-borne Encephalitis	
Also Known As:	Russian spring-summer encephalitis (RSSE), Taiga encephalitis, Far East Russian encephalitis
Principal Vector:	*Ixodes persulcatus* tick
Principal Hosts:	Small mammals (eg, rodents, squirrels), large vertebrates (eg, deer, elk, domestic animals); bird infection has also been demonstrated
Geographic Distribution:	Far eastern Russia (former USSR provinces of Primorie, Khabarovsk, Krasnojarsk, Altai, Tomsk, Omsk, Kemerovo, Ural, Priural, and western Siberia)
Seasonal Transmission:	May to August
Incubation Period in Humans:	10 to 14 d
Severity of Disease:	Severe
Major Clinical Manifestations:	Fever, headache, nausea, meningeal irritation with aseptic meningitis; flaccid lower motor neuron paralysis of upper extremities and bulbar centers; may be indistinguishable from poliomyeltis
Case Fatality Rate:	8%–54%
Vaccine Available:	Yes
Western Tick-borne Encephalitis	
Also Known As:	TBE, Central European TBE (CEE), Czechoslovak TBE, diphasic milk fever, biphasic meningoencephalitis
Principal Vector:	*Ixodes ricinus* tick
Principal Hosts:	Small mammals (eg, rodents), large vertebrates; unique is infection of and transmission of virus in the milk of goats, sheep, and cows
Geographic Distribution:	Czech Republic, Slovakia, Austria, Bulgaria, Romania, former Yugoslavia, Hungary, former USSR, Finland, France, Germany, Greece, Italy, Sweden, Switzerland
Seasonal Transmission:	Spring, summer, autumn
Incubation Period in Humans:	7 to 14 d
Severity of Disease:	Moderate
Major Clinical Manifestations:	A monophasic or biphasic illness characterized by fever, headache, nausea, anorexia, with the development of aseptic meningitis, encephalitis, or encephalomyelitis; remission can occur 4 to 5 d into illness but is followed by neurologic involvement (2^{nd} phase); long-term neurologic complications are infrequent
Case Fatality Rate:	1%–5%
Vaccine Available:	Yes
Powassan Encephalitis	
Also Known As:	POW
Principal Vector:	*I marxi, I cookei, I spinipalpus, Dermacentor andersoni* ticks
Principal Hosts:	Squirrels, porcupines, groundhogs
Geographic Distribution:	North America, Russia, Asia
Seasonal Transmission:	Spring, summer
Incubation Period in Humans:	1 or more wks
Major Clinical Manifestations:	Fever, headache, sore throat, somnolence, encephalitis; long-term neurologic complications can occur, including hemiplegia
Severity of Disease:	Severe
Case Fatality Rate:	10.5%
Vaccine Available :	No

Louping Ill

Also Known As:	——
Principal Vector:	*I ricinus* tick
Principal Hosts:	Small mammals, cattle, pigs, deer, sheep
Geographic Distribution:	England, Scotland, Wales
Seasonal Transmission:	Spring, summer
Incubation Period:	1 or more wks
Severity of Disease:	Mild
Major Clinical Manifestations:	Fever, lymphadenopathy, flu-like illness with development of mild meningoencephalitis without neurologic complications
Case Fatality Rate:	Minimal
Vaccine Available:	Yes

Kyasanur Forest Disease

Also Known As:	——
Principal Vector:	*Haemaphysalis spinigera* tick
Principal Hosts:	Small vertebrates
Geographic Distribution:	Karanataka State, India
Seasonal Transmission:	Dry season (January-April)
Incubation Period in Humans:	1 or more wks
Major Clinical Manifestations:	Fever, headache, pulmonary infiltrates, gastrointestinal hemorrhage; biphasic illness may occur with the development of meningoencephalitis
Severity of Disease:	Severe
Case Fatality Rate:	10.5%
Vaccine Available:	No

Omsk Hemorrhagic Fever

Also Known As:	——
Principal Vector:	*D reticulatus, D marginatus,* and Ixodid ticks
Principal Hosts:	Wild muskrats
Geographic Distribution:	North America, Russia, Asia
Seasonal Transmission:	Spring, summer, autumn
Incubation Period in Humans:	3 to 7 d
Major Clinical Manifestations:	Headache, biphasic fever, hemorrhage of the nose and gastrointestinal tract, pneumonia, rash
Severity of Disease:	Moderate
Case Fatality Rate:	0.5%-3%
Vaccine Available :	Yes

Adapted from: Gresíková M, Calisher CH. Tick-borne encephalitis. In: Monath TP, ed. *The Arboviruses: Epidemiology and Ecology*. Vol 4. Boca Raton, Fla: CRC Press; 1989: 177–198.

ages of 15 and 40 years, with females at equal risk to males in populations where tick exposure is not sex biased. People living in rural areas are at higher risk. The most frequently infected individuals are forest workers, farmers, and vacationers traveling into endemic areas. Western subtype TBE can be acquired orally by consuming contaminated milk and milk products. Transmission via the milk of cows, sheep, and goats has been responsible for several outbreaks of this disease. Infection by the oral route presents as a milder form of illness than does infection by ticks.

The principal vector of Far Eastern TBE and Western

TBE are the ticks *I persulcatus* and *I ricinus*, respectively. Seasonal *I persulcatus* activity in far eastern Russia begins at the end of April and lasts until June. Tick infection rates with TBE have ranged from 3.4% to 9.4%.[315] Activity of *I ricinus* in Europe has two peak seasons, April through May and September through October. In certain geographic areas, peak tick activity may occur in June and August, with less activity in July. TBE infection in these ticks ranges from 0.07% to 6%.[316] Western TBE virus has been isolated from other ticks, including *I trianguliceps, I arboricola, Haemaphysalis inermis, H punctata*, and *Dermacentor marginatus*.[312] The life span of these ticks is approximately 3 years. Their principal hosts are small mammals, such as hedgehogs, shrews, and moles.[317] The high level of viremia achieved in these animals after infection maintains an ideal TBE virus reservoir. Large vertebrates, such as domesticated animals and humans, are incidental hosts and contribute little toward maintaining the virus in the environment.

A noninfected tick becomes infected with TBE virus after taking an infected blood meal (Figure 35-15). One to twenty-five days after infection, virus can be found in the gut, salivary glands, and ovaries of the tick.[318] Laboratory studies document prolonged viral persistence up to 9 months after infection. Virus is amplified in the tick population by transovarial transmission, by sexual transmission from infected male ticks to females, and by cofeeding of an uninfected tick with an infected tick on a nonviremic host.[319–321] Transstadial transmission (eg, nymph to larva, larva to adult tick) also occurs. The virus is transmitted to the vertebrate host by infected saliva; the efficiency of viral transmission depends on the length of feeding. Adults are more effective transmitters than nymphs and larvae. Feeding of infected ticks on birds, though documented, is of unknown epidemiologic significance. Under laboratory conditions, bats can be infected with TBE virus and maintain viremia for long periods.[312]

Western TBE virus can be isolated in the milk of infected goats, sheep, and cows 1 to 7 days after acute infection and transmitted to humans by the ingestion of raw infected milk or cheese.[322–326] This virus has been shown to be infectious in milk, as well as sour milk and cheese, for as long as 2 weeks at 4°C and in butter for 60 days at 4°C.[312]

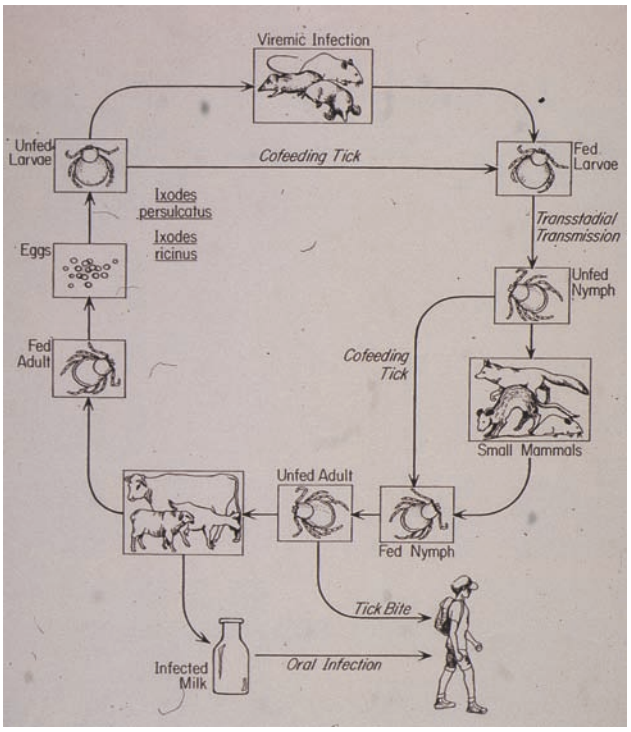

Fig. 35-15. The transmission cycle of tick-borne encephalitis showing the tick larvae becoming infected by feeding on a viremic host or by cofeeding with an infected larvae tick. Virus infection can occur throughout the life cycle of the tick by feeding on an infected host or by vertical transmission to its progeny. Infection and subsequent viremia of larger vertebrates perpetuate the transmission of virus to nymph and adult tick stages and eventually back to the host reservoir. As demonstrated, humans are dead-end hosts and do not contribute to the transmission cycle of TBE and become infected by the bite from an unfed infected adult tick or by drinking infected milk.
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Geographic Distribution

I persulcatus is the principal vector for Far Eastern subtype TBE and occurs in the far eastern part of Russia. The distribution of Western subtype TBE correlates to that of its principle tick vector, *I ricinus*; the disease occurs throughout the European part of Russia, Scandinavia, France, Germany, Poland, Austria, Switzerland, Italy, Romania, Hungary, Bulgaria, the Czech Republic, Slovakia, and the countries of the former Yugoslavia.[327] The most frequent occurrence of TBE and its tick vector is associated with humid, marshy, densely wooded areas.

Ixodes tick activity is greatest at an average temperature of 8°C to 11°C and an annual average rainfall of 800 mm.[316]

Incidence

Incidence rates of TBE are dependent on the degree of endemicity of the specific country, as well as geographic and meteorological conditions that affect the tick vector. The highest incidence of TBE is reported to be of the Far Eastern subtype from western Siberia, at an annual incidence of 11.7/100,000. The Ural mountain area has an incidence of 6.6/100,000.[311] An epidemiologic study of TBE performed in the Tribec region of Czechoslovakia (a highly endemic area for TBE) during the years 1953 to 1963 described an 11-year mean incidence of 19.3/100,000 and a peak incidence of 107.9/100,000 during 1955.[328] The highest age-specific incidence occurred in the 10- to 14-year-old age group, with an incidence of 33.2/100,000. Adult farmer and forestry workers were the occupational group at highest risk, with a rate of 21.3/100,000. TBE in this region coincided with the activity of the tick vector, which started in April and peaked during June. Incidence rates declined after June, with no cases seen after September. Of 67 patients infected with TBE during 1960 to 1963, 55.3% reported tick bite exposure only, 8.9% goat milk consumption only, and 22.3% both tick bite exposure and goat milk consumption; 13.5% had an unknown exposure. In 1,037 acute neurological cases observed in Hungary from 1963 to 1965, TBE was serologicaly confirmed in 23% of patients with encephalitis and 10% of patients with aseptic meningitis.[329] Germany, Switzerland, and Yugoslavia reported between 10 and 140 cases per year during the 1980s. Sweden experiences between 50 and 80 cases per year, with cases restricted to the archipelagoes and the coastal areas of the Baltic Sea. Austria experienced 400 to 700 cases per year in the 1980s, which declined to 81 cases per year after an active TBE campaign that vaccinated more than 5 million inhabitants.[307]

Serological surveys suggest that about 50% of TBE infections are subclinical. In endemic areas, seropositivity has been noted to reach 50% to 63% in individuals older than 55 years of age.[312] In a serosurvey conducted in Sweden,[307] clinical disease was estimated to have occurred in 6% against a background seroprevalence of 22%. In subpopulations with no clinically apparent TBE, the seroprevalence rate ranged between 4% and 12%.

Pathogenesis and Clinical Findings

The pathogenesis of this disease and reasons for asymptomatic versus severe disease are not known.

Far Eastern TBE

The Far Eastern subtype of TBE is the more severe clinical form of TBE, which manifests itself with the sudden onset of high fever, severe headache, nausea, vomiting, and photophobia after a 10- to 14-day incubation period.[312] An aseptic meningitis develops, which is manifested by nuchal rigidity and which progresses to changes in mentation and sensorium; this heralds the onset of encephalitis. Long-term neurologic sequelae can occur, such as hemiparesis, hemiplegia, and chronic progressive encephalitis, which may have an onset more than 10 years after primary infection.[330] Other complications of Far Eastern TBE infection include lower motor neuron paralysis, beginning with the upper extremities and progressing to the neck muscles and bulbar centers. Far Eastern TBE can present as a highly fatal (case-fatality rate of 29.2%) poliomyelitis type illness in 20% of cases.[331] Long-term residual complications of this form of TBE are spastic paresis of the lower extremities, epilepsy, and chronic encephalitis.

Western TBE

The Western subtype of TBE is the milder form of TBE and has a relatively low case-fatality rate of 1% to 5%[312] The incubation period is usually 7 to 14 days, though it may be as long as 28 days. Initial symptoms include headache, nausea, vomiting, anorexia, hyperesthesia, photophobia, and fever. The illness can also be biphasic. The first phase of illness lasts 4 to 6 days, followed by a variable period without symptoms. The second phase, which affects about 35% of cases, begins with spread of the virus to the central nervous system, manifested by a return of fever and the development of aseptic meningitis.[307] Long-term neurologic sequelae are uncommon, but complications of monoplegia and sensorineural deafness have been described.[332]

Powassan Encephalitis

Powassan encephalitis was first clinically described and the virus (POW virus) isolated from the brain of a child from Powassan, northern Ontario, who died of encephalitis in September 1958. Subsequent studies revealed that the virus was a member of the tick-borne flaviviruses closely related to TBE virus. POW virus has been isolated from four species of North American ticks: *I cookei*, *I marxi*, *I spiniplapus*, and *D andersoni*.[333] POW virus has also been isolated in Russia from the

following ticks: *H neumanii, I persulcatus*, and *D silvarum*. It is found in variety of small, wild vertebrates and in domesticated animals, such as dogs, cats, horses, cattle, and goats. POW virus has also been isolated in several species of birds in Russia and North America. The geographic distribution of POW virus is widespread in North America, with virus having been isolated in animals from Ontario, California, Colorado, Connecticut, Massachusetts, New York, South Dakota, and West Virginia. POW virus has also been demonstrated in Russia, China, and parts of Southeast Asia.[334]

Humans are incidental hosts for the infected ticks, and after an incubation period of 1 or more weeks, the clinical symptoms of fever, sore throat, headache, somnolence, disorientation, and nuchal rigidity occur.[334] Encephalitis, meningoencephalitis, or aseptic meningitis develop, with a case-fatality rate of 10.5%. There may be long-term residual neurologic deficits, including hemiplegia, muscle atrophy, and spasticity. The incidence of Powassan encephalitis is extremely low in North America; there have been 19 confirmed infections and no cases since 1981.[333] Patients vaccinated with TBE virus vaccine had low-titered cross-reactivity to POW virus at a level insufficient for protection.

Louping Ill

Louping ill virus is part of the TBE complex and is primarily a disease of sheep in Great Britain.[335] Infection can also occur in cattle, pigs, and deer. The virus is transmitted by the bite of the tick *I ricinus*.[318] Infection in humans can occur by the bite of infected ticks or by contact with infected tissues of diseased animals. Butchers and veterinarians are at highest risk for acquiring infection. Human disease presents with fever, lymphadenopathy, and flu-like symptoms. A mild meningoencephalitis can occur, but neurologic complications are rare.[334] The case-fatality rate is extremely low. A formalin-inactivated vaccine is available for animals and humans who are at high risk of exposure.

Omsk Hemorrhagic Fever

Omsk hemorrhagic fever is a subtype of the TBE complex described in the Omsk province of the former Soviet Union. The spring–summer pattern of disease depends on the activity of this virus's tick vectors, *D reticulatus* and *D marginatus*.[84] Ixodes ticks are also vectors. There is an incubation period of 3 to 7 days, followed by the onset of headache and a biphasic fever. Gastrointestinal bleeding and hemorrhage, bronchopneumonia, and rash can occur. Case-fatality rates are 0.5% to 3%. A vaccine for Omsk hemorrhagic fever is available in Russia.

Kyasanur Forest Disease

Kyasanur Forest disease (KFD) virus is a subtype within the TBE complex first described in 1957 in Karnataka State, India.[84] There are approximately 400 to 500 cases per year there. The highest incidence occurred in 1983: 1,555 cases and 150 deaths, producing a case-fatality rate ranging from 5% to 10%.[336] KFD virus and disease are found in the towns of Saga and Sorab in Shimoga District, Karnataka State, India. Serological surveys of this district demonstrated neutralizing antibody to KFD in 2 of 287 individuals tested. Antibodies to KFD have been detected in animals and humans from the semiarid areas of Saurashtra and Kutch, India, which are 700 miles from the KFD focus.[337] The tick vector is *H spinigera*. The virus is maintained in small vertebrates; humans and primates are incidental hosts. Clinical disease in humans is manifested by fever, headache, and severe myalgias, but gastrointestinal hemorrhage and pulmonary involvement can also occur. A biphasic course of illness can be seen with an initial prodromal phase, followed by a 1- to 2-week period of remission, followed by clinical illness. Meningoencephalitis can occur with no long-term residual effects.

Diagnostic Approaches

The differential diagnosis of early TBE is broad and includes a number of etiologies for acute meningitis and early encephalitis, to include *Streptococcus pneumonia, Neisseria meningitidis, Listeria monocytogenes,* herpes simplex 1 and 2, enteroviruses, and adenovirus. As the disease progresses and becomes consistent with a viral encephalitis by clinical and laboratory findings, the differential of potential etiologies narrows but continues to include viral pathogens such as the ones that cause polio, mumps, St. Louis encephalitis, Western equine encephalitis, Venezuelan equine encephalitis, and lymphocytic choriomeningitis and the human immunodeficiency virus. Essential to making an accurate and expedient diagnosis is an awareness of local disease threats and epidemiology, a history of tick bite or exposure or ingestion of unpasteurized milk products, and laboratory support that can test for TBE.

Viral isolation and identification is the gold standard for diagnosis. TBE virus can be isolated in serum during the viremic phase of illness. All specimens should be stored at -70°C. Virus can also be isolated by intracranial inoculation of infected serum or tissue into suckling mice or plaque assay in Vero cells.[84,312] Chick embryo cell cultures may also be used. Viral isolation in ticks can be accomplished by suspending 5 to 10 adult ticks in 1 mL of Eagle's medium with 10% heat-inactivated bovine serum.

Serologic diagnosis is by virus neutralization (the most specific method), complement fixation, hemagglutination inhibition, EIA, or indirect hemagglutination.[84,312] IgM antibody capture EIA of serum is the test of choice for acute infection.[338] A high IgM titer or a 4-fold increase in serum IgG as measured by complement fixation or hemagglutination inhibition between acute and convalescent serum provides convincing evidence for TBE infection. Rapid identification of TBE virus by the fluorescent antibody technique and an enzyme-linked immunosorbent assay have also been described.[339,340] Antibody-based assays can give false-positive results due to the cross-reactivity of TBE with flaviviruses in general and with other flaviviruses within the TBE complex in particular. Individuals previously vaccinated against yellow fever or Japanese encephalitis may also cross-react. Reverse transcription polymerase chain reaction has been developed for the rapid detection of TBE viruses and offers the opportunity for rapid diagnosis with a high degree of sensitivity and specificity in the field.[341]

Recommendations for Therapy and Control

Treatment of TBE infection is supportive, with emphasis on protecting the airway and providing ventilatory support if needed. There is no literature for or against the use of steroids. As with other viral infections, the use of salicylates may be contraindicated in the pediatric population because of the risk of Reye's syndrome. A TBE immune globulin is available in Austria and Germany for passive immunization and preexposure and postexposure prophylaxis of TBE (FSME-Bulin, Baxter Immuno AG, Austria). This is a hyperimmunoglobulin concentrate containing TBE-specific immunoglobulin at a titer of 1:640 as measured by hemagglutination inhibition. It is reported to be 60% to 70% effective when given within 96 hours of exposure; protection is manifest within 24 hours of administration and for 4 weeks thereafter. Four days after exposure, the prophylactic efficacy of TBE immune globulin diminishes, and clinical disease may actually be exacerbated by its administration.[342] TBE immune globulin should not be administered for 28 days (the maximal TBE incubation period) after the window of potential benefit.

Vaccine

The Far Eastern TBE virus was isolated in 1937 and developed by Zilber into an inactivated mouse brain–derived vaccine used to vaccinate Russian troops. In 1950, a vaccine against the western strain of TBE was developed by Danes and Benda in Czechoslovakia and found to be highly effective in human volunteers, causing few hypersensitivity reactions.[343] TBE was further modified into a highly purified, killed vaccine with few side effects, which resulted in the licensure of an Austrian TBE vaccine named FSME-Immun. Other inactivated whole virus TBE vaccines that are commercially available or are in development are the TicoVAC vaccine (Baxter AG, Vienna, Austria), Enceput (Behringwerke AG, Marburg, Germany), and the Cultural Purified Concentrated Inactivated Freeze-dried Tick-borne Encephalitis Vaccine (Institute of Poliomyelitis and Viral Encephalitides, Moscow, Russia).[344–346]

Trials with FSME-Immun demonstrated antibody production in 93% of vaccine recipients after two vaccinations and 100% after the third dose. Pyrexia occurred in 4% to 10% of recipients, local pain in 23% to 58%, malaise in 19% to 33%, and headache in 14% to 33%.[347] Neutralizing antibodies were achieved after a three-dose schedule in all volunteers; cross-neutralizing antibodies were present for both Far Eastern and Western TBE isolates from 12 geographic regions and for louping ill virus.[348] A multinational phase II study with this vaccine using two dose schedules (an abbreviated schedule with 0.5 mL given intramuscularly [IM] on days 0, 7, and 21 or the conventional schedule on days 0, 28, and 300) showed both to be equally immunogenic.[349] Active TBE immunization in nonimmune volunteers demonstrated an IgG antibody response comparable to that seen after natural infection.[350] Intradermal administration of FSME Immun demonstrated quicker seroconversion and higher antibody levels than achieved by intramuscular injection.[351,352] Serious side effects from FSME Immun are rare. Only 15 cases of mild meningoencephalitis and 1 case of myelitis have been reported.[353]

Side effects with Encepur have been reported and include asthenia, back pain, chills, flu syndrome, fever, lymphadenopathy, arthralgia, headache, and pain at the injection site.[354] Fever following vaccination with this vaccine was a frequent finding

though adverse events were less frequently observed following the second dose of vaccination.[355] Adverse reactions have also been observed with the TicoVac vaccine, especially with high fevers in very young children who received the vaccine.[356] This resulted in the recommendation by Germany's Federal Agency for Sera and Vaccinations that this vaccine not be used in children under 3 years of age.

Countries that experience high rates of TBE have pursued widespread immunization campaigns using TBE vaccine.[307] Currently, no TBE vaccine is licensed by the US Food and Drug Administration (FDA). FSME-Immun is available as an investigational new drug with the FDA under a protocol filed by the US Army Medical Research and Materiel Command. Under this protocol, vaccine is available to US military personnel going to TBE-endemic areas and considered to be at high-risk for infection.[357]

The current recommended vaccination schedule of FSME-Immun consists of a 0.5 mL intramuscular (IM) dose at days 0 and 28 and at 1 year. One 0.5 mL dose contains 2 μg of viral antigen, 1 mg of $Al(OH)_3$, less than 0.6 mg of human albumin, less than 0.005 mg of formaldehyde, and less than 0.05 mg of the preservative merthiolate. An abbreviated schedule of 0.5 mL IM at days 0, 7, and 21 may be used with equal efficacy.[342] An accelerated schedule was used in US military deployed in Bosnia using a three-dose schedule delivered at 0, 7, and 28 days with an 80% seroconversion rate.[357] Few side effects were noted with this dosing schedule with a 0.18% rate of self-limited symptoms. Intradermal administration has been demonstrated to be more effective than intramuscular dosing.[351,352] A booster dose of the IM vaccine is recommended every 3 years.[312]

Current contraindications for the administration of TBE vaccine include having an acute febrile illness or having a history of allergies to any of the vaccine components, including egg albumin. A merthiolate-free vaccine is available for patients allergic to this chemical. The vaccine is safe for pregnant and lactating women.

Personal Protection

Personal protection is the mainstay to prevent TBE infection. Insect repellent with DEET (N,N-diethylmeta-toluamide), permethrin-impregnated clothing, long shirts worn with cuffs buttoned, pants worn tucked into boots, and daily tick surveys are all effective measures. Avoidance of unpasteurized milk and milk products is also recommended. Tick control by insecticide spraying of local endemic areas has also been effective in eradicating the tick and the virus.

Preparation of safe milk products requires 30 minutes or more of pasteurization at 65°C, pasteurization at 80°C for 1 minute, or boiling for longer than 1 minute.

[Timothy P. Endy]

SANDFLY FEVER

Introduction and Military Relevance

Sandfly fever is a self-limited, febrile, viral illness transmitted by biting flies of the genus *Phlebotomus*.[358] It occurs in Africa, Europe, and Asia with seasonal incidence peaking between April and October.[359] The military significance of sandfly fever is magnified because its short incubation period makes it capable of rendering large numbers of nonimmune service members ineffective during an operation while the native populace remains largely immune and unaffected.[360,361] Sandfly fever has attacked nonimmune troops in epidemic proportions when they are stationed in an area where the virus is endemic.

Accounts by British military surgeons during the 19th century of epidemic febrile illness among British troops stationed in various locales around the Mediterranean Sea have been cited as accurate clinical descriptions of sandfly fever.[362–364] In 1905, Taussig[365] provided epidemiologic evidence to support the popularly held belief that the midges known as pappataci flies (*Phlebotomus papatasi*) were connected with the 3-day fever that afflicted Austrian troops every summer by the Adriatic Sea. The disease was commonly called pappataci or phlebotomus fever.

In 1909, the etiologic agent of sandfly fever was identified in the classic investigations by the Austrian military commission of Doerr, Franz, and Taussig.[366] These investigators reproduced the disease in humans by inoculating volunteers living in areas free from the disease with blood obtained from patients on the first day of fever. The Austrian commission also established that the infectious agent was filterable and that *P papatasi* was the vector of the illness.

Description of the Pathogen

The agent, Sandfly fever virus, belongs to the family *Bunyaviridae*, genus *Phlebovirus*.[367] Like other

viruses in *Bunyaviridae*, Sandfly fever virus possesses negative-sense, single-stranded RNA segments designated as small (S), medium (M), and large (L). It has three major structural proteins: two surface glycoproteins encoded by the M segment that project from the virion's lipid bilayer envelope and a nucleocapsid protein encoded by the S segment.

Sandfly fever virus is recovered most easily in Vero cells, where it demonstrates both cytopathic effect and plaques under agar. Field isolates of Sandfly fever virus have demonstrated poor infectivity in various laboratory animals in previous studies. These studies have failed to demonstrate pathogenicity of the virus for mice, hamsters, rats, rabbits, guinea pigs, or monkeys.[367–370] Although intracerebral injection of Sandfly fever virus is lethal to suckling mice, similar effects in adult mice can be demonstrated only after serial passage and adaptation to mouse brain.

Seminal investigations by Sabin in the 1940s demonstrated that two virus isolates, from Sicily and Naples, were antigenically distinct. Cross-protection experiments[371] demonstrated that immunity is strain-specific (Naples *vs*. Sicilian) and that a single infection gives solid protection against the same antigenic type. That is to say, patients are immune to subsequent intravenous challenge with homologous wild-type Sandfly fever virus. Sabin's challenge experiments also demonstrated the duration of immunity to be at least 9 years. A seroprevalence study[372] demonstrating the longevity of neutralizing antibody following natural infection with a given strain suggests that immunity is probably lifelong.

There are more than 20 viral isolates from phlebotomine flies in both the Eastern and Western hemispheres that are antigenically related to Sandfly fever virus and that cause infrequent cases of human disease.[373–375] Toscana virus represents a *Phlebovirus* strain that is distinct from, albeit related to, Naples serotype[376] and that has been reported as a cause of aseptic meningitis in Portugal,[377,378] Cyprus,[379] and the Tuscany and Marche regions of Italy.[380] Sandfly fever virus Sicilian and Naples, however, are the two most important strains epidemiologically, both having caused recurrent epidemics among military populations.

Epidemiology

Transmission

The deployment of military service members to a foreign country entails their intimate contact with its natural environment, which may include sand flies. The destruction of property and breakdown in public health measures that inevitably accompany warfare are important epidemiologically, as has been shown by the frequent clustering of sandfly fever cases around areas of rubble and debris—good breeding habitats for *Phlebotomus* species.

The sand fly seeks a blood meal in the early evening and is small enough to penetrate mosquito netting. The extrinsic incubation period in the vector is approximately 7 to 10 days. Although the fly will take a blood meal from a variety of species (eg, humans, cattle, canines, equines, birds),[381] the virus and its vector may also persist via autogeny (the ability to lay eggs in the absence of a blood meal). Despite demonstration of infection by Sandfly fever group viruses in some animals,[373] a vertebrate reservoir has yet to be demonstrated. Serosurveys have suggested that small mammals may have antibody to certain viral strains, but the significance of this finding to the maintenance of the disease is uncertain.[382] During epidemics, humans may also serve as viremic vertebrate hosts in a human-*Phlebotomus*-human cycle. The virus is vertically, or transovarially, transmitted in sand flies,[383–385] a phenomenon that is important to the maintenance of endemic disease, but decline of virus infection rates in successive generations suggests that these agents may not be maintained indefinitely in the insect vector by this mechanism.[386]

Sandfly fever occurrence is distinctly seasonal, with the highest incidence occurring during the late spring and summer months, depending on the prevailing temperatures and timing of the rainy season.[387] This distinct seasonality probably accounts for the lack of reported cases during the Persian Gulf War in northern Saudi Arabia and southern Iraq. The virus can overwinter either via transovarial transmission[388] or diapause in the fourth larval stage.[389]

Geographic Distribution

Sandfly fever has a wide geographic distribution in those parts of Europe, Africa, and Asia between 20° and 45° North latitude, reflecting the range of *P papatasi*.[359,390] This vector breeds in dry, sandy areas near rubble or debris and in the nooks and ceiling corners of buildings. The disease persists mainly in the lower altitudes of subtropical and tropical countries in which there are long periods of hot, dry weather.

Studies[373,391–393] have discovered other phlebo-viruses that are serologically related to Naples and Sicilian types and are broadly distributed in Eurasia

and the Americas. These viruses have been recovered from phlebotomine flies of the genus *Lutzomyia*, as well as from mosquitoes. Several of these phleboviruses (eg, Chagres, Alenquer, Candiru, Punta Toro viruses) may cause a nonspecific febrile illness in humans similar to sandfly fever.[394–396]

Incidence

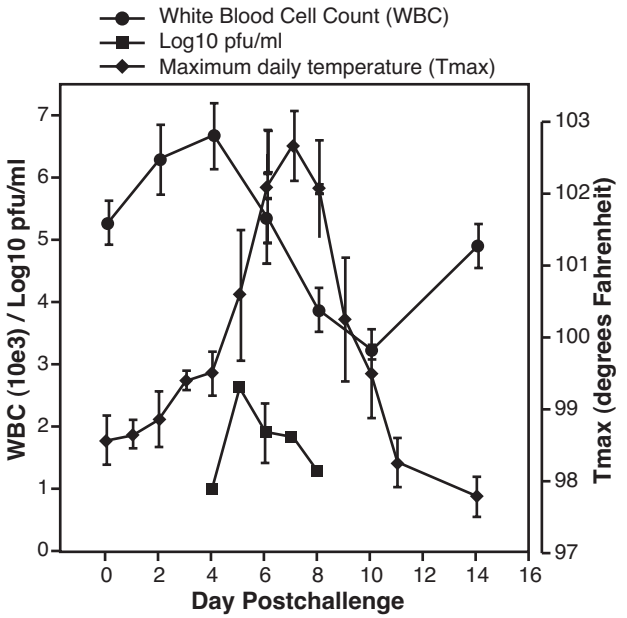
The recurrent problem with phlebotomus fever in the earlier half of this century prompted study by several British military commissions.[397] During World War II, there were 19,000 cases of sandfly fever, with the highest incidence reported in the Middle East theater. Attack rates were 3% to 10% of all troops, although in some units the attack rate was greater than 50%. During the Sicily campaign in the summer of 1943, the 7th US Army sustained approximately 8,500 cases of sandfly fever, constituting more than half of the medical battalion's workload once the number of casualties dropped off after the first 10 days of the invasion. In the Persian Gulf Command, the attack rates were 50% higher than those in the Middle East as a whole and reached a peak of 235 cases per 1,000 men in August 1942. These epidemics instigated a US Army investigation in 1943 and 1944 led by Major Albert Sabin.[370]

The disease can also be a problem for hospital personnel, as was illustrated by four hospital-centered outbreaks in the Middle East during World War II.[360,387] In these epidemics, 25% of all doctors and nurses and nearly 100% of other hospital personnel were affected. Twenty percent of the nearly 2,000 patients admitted with other diagnoses contracted sandfly fever while in the hospital.

Outbreaks in the 1980s in United Nations troops in Cyprus[398] and Russian soldiers in Afghanistan[360,399] demonstrate sandfly fever's continued potential for significant morbidity. The fact that both Sicilian and Naples strains are distributed widely in the Middle East, which has been a focal point of American economic and political policy for the past quarter century, reemphasizes this disease's military relevance.

Pathogenesis and Clinical Findings

The clinical manifestations of sandfly fever were extensively documented by Sabin in the 1940s.[369] In the course of experimentally inducing more than 100 cases of sandfly fever, Sabin and his coworkers demonstrated the clinical illness as well defined and self-limited (hence the name "3-day fever"), having a very predictable clinical course, and with no mortality or sequelae.[370] Indeed, the relatively uniform nature of the classic febrile syndrome of sandfly fever has made it a model in the study of viral and febrile illnesses.[400] After an incubation period of 2 to 6 days, a fever of 39°C (102°F) or higher develops in two thirds of patients (Figure 35-16). The duration of fever is from 1 to 4 days in 85% of patients and is accompanied by a frontal or retroorbital headache, malaise, myalgias, anorexia, lymphopenia, and viremia. In addition, many will also have low back pain, photophobia, and nausea. A smaller percentage may suffer from arthralgias, odynophagia, or vomiting. Infrequently, a patient may experience abdominal pain lasting 1 to 2 days. On physical examination, persons with sandfly fever appear flushed and often have conjunctival injection (Figure 35-17).



PFU: Plaque-forming units

Fig. 35-16. The temporal correlation of fever (degrees Fahrenheit), neutropenia (granulocytes x 10^3 cells / mm^3), and viremia (PFU / ml) in a typical course of sandfly fever.

The most distinctive laboratory feature of sandfly fever is leukopenia, which occurs in approximately 90% of patients.[400,401] Characteristically, on the first day of fever there is a normal total white blood cell (WBC) count with an absolute lymphopenia (400-900 cells per milliliter) and a corresponding increase in neutrophils, including immature forms. Within 2 to 3 days of resolution of the fever, a leukopenia averaging 3,000 WBC per milliliter (range 2.5–3.5 x 10^3 WBC per milliliter) develops as neutrophils diminish and lymphocytes

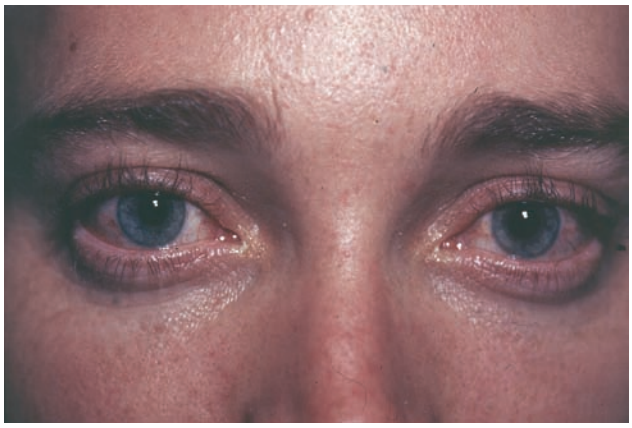


Fig. 35-17. Although neither specific nor universal for sandfly fever, this patient's conjunctival injection illustrates why the disease earned the appellation "Hundskrankeit" (hound fever) when first characterized by Taussig.* This stage of the illness renders the patient bedridden for 2 to 4 days and is accompanied by moderately severe fever, chills, headache, myalgias, and malaise.
Photograph: Courtesy of Dr. David McClain.
*Taussig S. Die Hundskrankheit, endemischer Magankatarrh in der Herzegowina. *Wien Klin Wchnschr.* 1905;18:129–136,163–169.

increase their relative percentages in the differential WBC count. Slight decrements in patients' platelet counts, as well as mild elevations of the liver transaminases and alkaline phosphatase, may also occur during the febrile period and rapidly return to normal after cessation of fever.

Toscana virus has been clearly implicated in summer cases of aseptic meningitis, although it also causes subclinical or asymptomatic infections.[402,403] Both the clinical and cerebrospinal fluid findings in these meningitis cases were those of a viral syndrome with aseptic meningitis, with no specific features to distinguish them from enteroviral or other viral etiologies. Assertions that other serotypes of the Sandfly fever virus group may cause meningitic inflammation remain unproven.[404]

Diagnostic Approaches

Given the relatively nonspecific nature of the clinical illness, sandfly fever must be suspected when patients in an endemic area have a short-lived (2 to 4 days) viral syndrome with prominent fever, malaise, and headache. Epidemic illness among expatriates that spares most of the native populace is especially suggestive. Viremia is relatively low titer (1-3 $\log_{10}$ plaque-forming units) and runs concurrently with the fever; it is within the sensitivity of classic viral isolation procedures or polymerase chain reaction but not detectable by antigen-capture enzyme-linked immunosorbent assay (ELISA). Serologic diagnosis may be made by detecting a 4-fold rise in neutralization or ELISA titers between acute and convalescent sera or by the demonstration of IgM antibody acutely. Both ELISA and neutralizing antibodies appear within 2 weeks after acute infection.[368]

Recommendations for Therapy and Control

Palliation for the clinical symptoms of sandfly fever may be achieved with antipyretics and analgesics. Despite its in vitro activity against the virus, oral ribavirin failed to prevent the disease (McClain DJ, Summers PL, Byrne R, Huggins JW, unpublished data, 1997).

The most useful countermeasure against sandfly fever at present remains vector control of *Phlebotomus* species. Pesticides were effectively used in Italy after World War II to control the transmission of the virus.[372] The larvae develop in shaded microhabitats that contain their requirements for darkness, humidity, and organic matter.[405] Therefore, pesticide control should target areas such as stables, poultry houses, animal burrows, and crevices in rock and masonry. For example, the spraying of animal burrows and termite mounds with cyfluthrin will provide short-term area control of adult sand flies.[406] The flight range of sand flies is limited to a few hundred meters from their breeding and resting sites, often resulting in a rather focal distribution.[407] Notably, the mesh in mosquito netting is too big to exclude sand flies. Using permethrin-treated screens is only partially effective in reducing sandfly populations within a dwelling.[408]

Although experience with a related *Phlebovirus*-caused disease, Rift Valley fever, indicates that a vaccine that induces neutralizing antibody will protect against disease,[409] at present there is no available sandfly fever vaccine.

[David J. McClain]

LYME DISEASE

Introduction and Military Relevance

Lyme disease is a rapidly emerging infectious disease (Figure 35-18). Both European and American literature describe a wide array of clinical symptoms associated with those of Lyme disease since

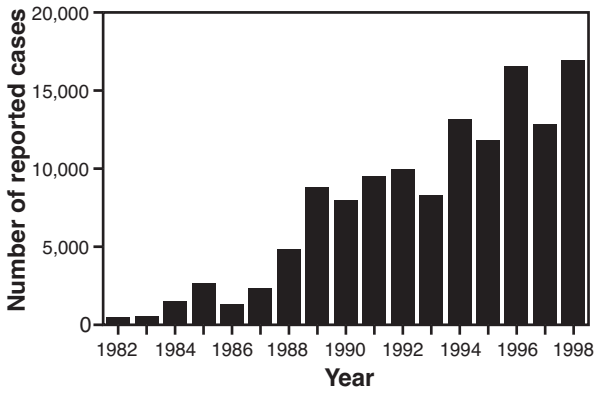


Fig. 35-18. The number of reported cases of Lyme disease by year in the United States, 1982 through 1998. Source: Centers for Disease Control and Prevention. Surveillance for Lyme disease—United States, 1992—1998. *MMWR*. 2000;49(SS03):1–11.

the 1900s.[410,411] Since the initiation of surveillance by the Centers for Disease Control in 1982 and its designation as a nationally notifiable disease in January 1991, Lyme disease has become the most common vector-borne disease in the United States.[412] The relative ease of contracting this tick-borne spirochetal disease, difficulties in its diagnosis, controversies in its management, and occurrence of debilitating manifestations in chronic Lyme disease and post-Lyme syndrome make this disease a significant public health issue for both civilians and the military.

US military personnel are at increased risk for contracting this disease because their training, combat, and humanitarian assistance missions, as well as recreational activities such as hiking, hunting, and camping, bring them in contact with the disease vectors. Several outbreaks of Lyme disease have occurred at military installations and in military personnel. Of 117 persons who acquired Lyme disease in New Jersey from 1978 to 1982, 30 were exposed to ticks at the Naval Weapons Station Earle in Monmouth County.[413] Isolation of the etiologic agent in animal reservoirs and tick vectors established Fort McCoy, Wisconsin, a military field training camp, as a highly endemic area.[414] Among military personnel reported with Lyme disease from North Carolina and Virginia in 1989, the majority of cases were exposed during field operations or training at Camp Lejeune, NC, and Quantico, VA.[415] Other high-risk sites include Fort A.P. Hill, Virginia, and Fort Chaffee, Ark. The mobility of military personnel also increases the chances that they will be exposed in one part of the world and develop illness in another part. Reports of cases have been published from both Germany and the United States in which the infection was acquired in the United States but the patient came down with the disease in Germany and vice versa.[416,417]

Description of the Pathogen

The causative agent, *Borrelia burgdorferi,* was identified as a spirochete in 1982 by Burgdorfer and colleagues.[418] Borreliae are corkscrew-shaped bacteria resembling other members of the family *Spirochaetaceae*. They are best visualized under phase-contrast or darkfield microscopy. They do not live in soil, water, or plants and are not transported by fecal contamination or aerosols.[411] They have complex nutritional requirements, making growth in culture difficult.

Epidemiology

Transmission

Borrelia burgdorferi is transmitted to humans through the bite of infected ticks, specifically certain members of the *Ixodes* species complex of the hard-bodied ticks. Several species of this complex transmit *B burgdorferi* to humans: *I scapularis* (in the northeastern, upper midwestern, and southeastern United States),[419] *I pacificus* (the West Coast of the United States),[420] *I ricinus* (in Europe),[421] and *I persulcatus* (in Asia).[422] The Lone Star tick (*Amblyomma americanum*) also has been found to contain the spirochete, but it is not clear that it can transmit the infection to humans.

Ixodes scapularis, also known as the deer tick, is the most common vector of Lyme disease in the United States. (The name *I dammini,* which was used to describe the deer tick in the northeastern United States, was relegated to a junior synonym of *I scapularis* upon finding that the deer tick of the northeastern and southeastern United States are the same species.) *I scapularis* has a 2-year life cycle, in which environmental cues trigger its host-seeking activity. The larval and nymph stages of deer ticks are parasites of a wide variety of vertebrate species (eg, mice, passerine birds, chipmunks, voles, squirrels, raccoons, foxes, deer, and other mammals). The white-footed mouse (*Peromyscus lecopus*), chipmunks (*Tamais striatus*), and passerine birds—including American robins (*Turdus migratorius*), common grackles (*Quiscalus quiscala*), Carolina and house wrens (*Thryothorus ludovicianus, Troglodytes aedon*), ovenbirds (*Siiurus aurocapillus*), and common yel-

lowthroats (*Geothlypis trichas*)—serve as competent reservoirs of the spirochete in nature, especially when larval and nymphal ticks co-feed in close proximity.[414,423–426] Since many people in the Northeast are exposed to nymphal ticks on their residential lawns, passerine birds are the probable contributing hosts.[424] In some areas, more than 40% to 50% of white-footed mice, chipmunks, and birds are infected with *B burgdorferi*.[425–427] White-tailed deer (*Odocoileus virginianna*) also may be competent hosts for immature stages, though several other researchers disagree.[428–430] Adult ticks show a preference for larger animals, particularly the white-tailed deer. Adult ticks mate while they are feeding on the deer.

In the western United States, *I pacificus,* the Western black-legged tick, is the major vector of *B burgdorferi*.[431] Reservoir hosts include the dusty-footed wood rat *(Neotoma fuscipes*), mice (*Peromyscus* ssp.), other rodents, and perhaps passerine birds.[431–432] Columbian black-tailed deer *(Odocoileus hemionus columbianus*) and carnivores are the major host for adult *I pacificus*.[433]

Increasing cases of Lyme disease occur as humans increase their contact with nature. Ticks prefer a relatively humid (85%) environment in mixed hardwood woodlands near creeks, river valleys, lakes, and coastal areas.[410] These are the same areas people tend to select for recreational areas and residential communities. During the 18th and 19th centuries, deer were hunted to near extinction, and their forest habitats were turned into farmland. Recent ecological efforts, hunting regulations, and reversions of marginal farms to woodlands have been favorable for deer populations, which have increased from a low of approximately 350,000 at around 1900 to more than 18 million in 1992. The

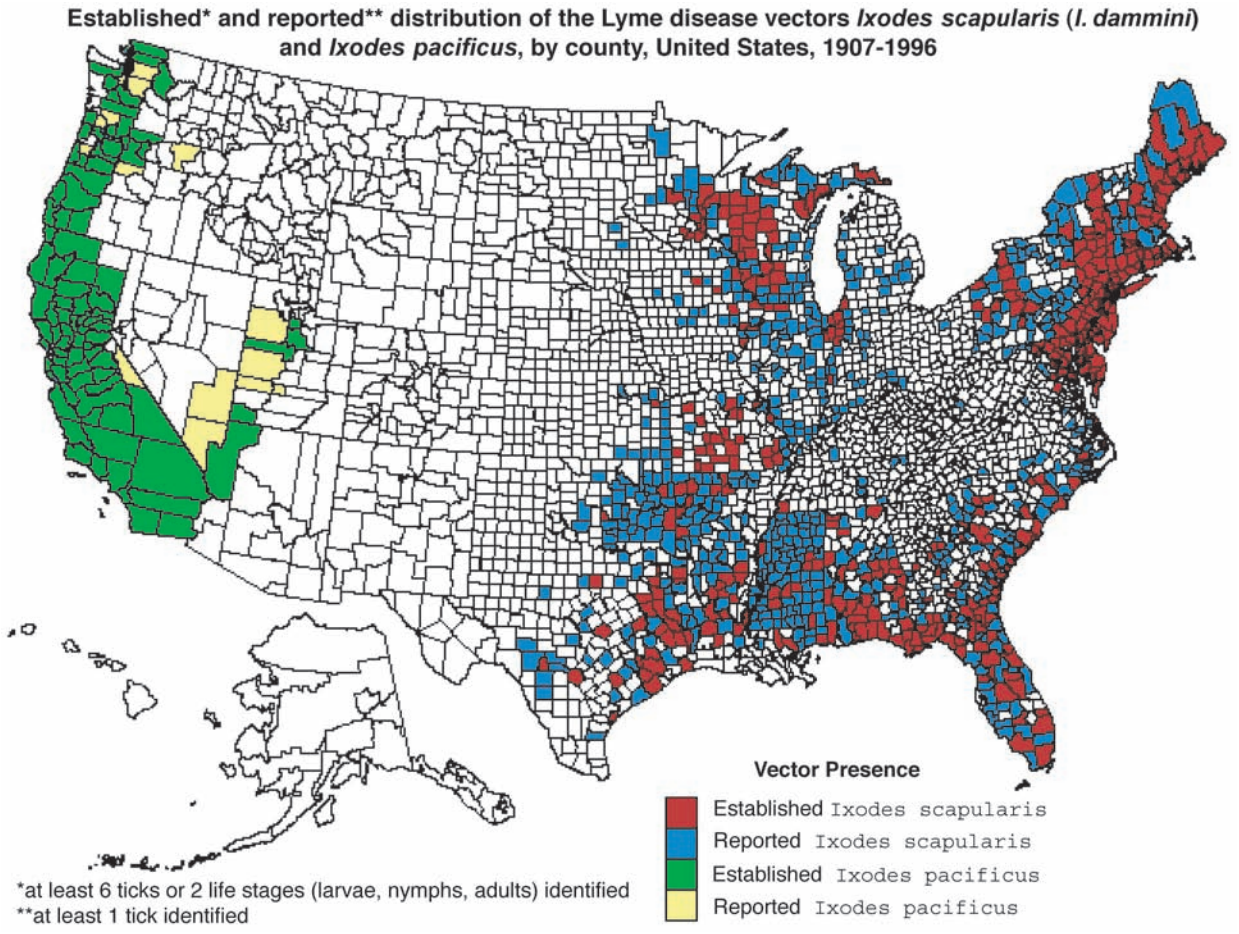


Fig. 35-19. The established and reported distribution of the Lyme disease vectors *Ixodes scapularis* (*I dammini*) and *Ixodes pacificus*, by county, in the United States from 1907 through 1996. Source: Centers for Disease Control and Prevention. CDC Lyme Disease web page. http://www.cdc.gov/ncidod/dvbid/tickmap.htm. Accessed on 16 Sept 1998.

increase in the deer population has led to an increase in the deer tick population and contributed to the emergence of Lyme disease.[434] A many-fold increase in the population of the immature *I scapularis* ticks was reported from 1984 to 1991.[419]

Experimental studies have suggested that the duration of bite required for transmission of *B burgdorferi* is 24 to 48 hours.[435] The spirochetes, which reside in the tick's midgut, begin to multiply after the tick starts to feed, and they migrate into the salivary glands and enter the host's skin as the tick continues to feed. This process requires about 24 hours. This time lag between onset of the bite and transmission of *B burgdorferi* allows for preventive measures to be taken against Lyme disease.

Geographic Distribution

Lyme disease is reported in most temperate regions, to include North America, Europe, Asia, and South Africa.[436–441] It is reported from all states in United States except Alaska and Montana; the Northeast and upper Midwest are areas of heavy concentration. Moderate risk of Lyme disease is also seen in the Pacific Coast. Lyme disease distribution correlates closely with the white-tailed deer and deer tick populations[442,443] (Figure 35-19).

Incidence

The number of cases of Lyme disease reported to the Centers for Disease Control and Prevention (CDC) has increased since 1982 and exceeded 16,000 cases in 1996.[412] But this number is likely to be grossly underestimating the true incidence of Lyme disease. According to one estimate, only 11% to 16% of Lyme disease cases in their state were reported by Connecticut physicians in 1992.[444] On the other hand, Steere reported that 57% of 788 patients who were referred to a Lyme disease specialty clinic with a diagnosis of Lyme disease did not have the disease.[445] Most of these non–Lyme disease patients had either chronic fatigue syndrome or fibromyalgia. Such underreporting and misdiagnosis due to confusion with similar illnesses interfere in assessing the exact magnitude of the problem caused by Lyme disease.

Pathogenesis and Clinical Findings

The body's immune response to the spirochete may be classified into acute localized disease, acute disseminated disease, chronic disease, and post-Lyme syndrome. The acute disease occurs from 2 days to 2 weeks after a tick bite. The classic finding of erythema migrans (Figure 35-20), an expanding annular erythematous skin lesion with central clearing, develops at the site of the tick bite in 50% to 75% of patients. Additional satellite lesions may occur. The majority of patients with EM also experience systemic symptoms (eg, fever, malaise, headache, stiff neck, fatigue), but these flu-like symptoms may occur without EM.

Hematogenous spread allows dissemination of the spirochete to the rest of the body within the first few weeks of the infection. This acute disseminated disease may manifest as multiple EM, acute meningitis, cranial neuropathies, myocarditis, cardiac conduction abnormalities, hepatitis, myositis, and frank arthritis. Symptoms suggestive of acute meningitis include malaise, fatigue, lethargy, headache, and neck stiffness. Unilateral or bilateral seventh cranial nerve involvement (eg, Bell's palsy) is the most common cranial neuropathy. Only 1% to 2% of patients with acute disseminated disease manifest cardiac abnormalities (eg, myocarditis, pericarditis, varying degrees of reversible atrioventricular block). Arthralgia affecting one or more joints is the most common sign of acute disseminated disease and lasts from hours to days.

Chronic Lyme disease is characterized by localized inflammation primarily of the nervous system, skin, and musculoskeletal system. Prominent focal central nervous system abnormalities, subtle cognitive dysfunction, and peripheral neuropathies

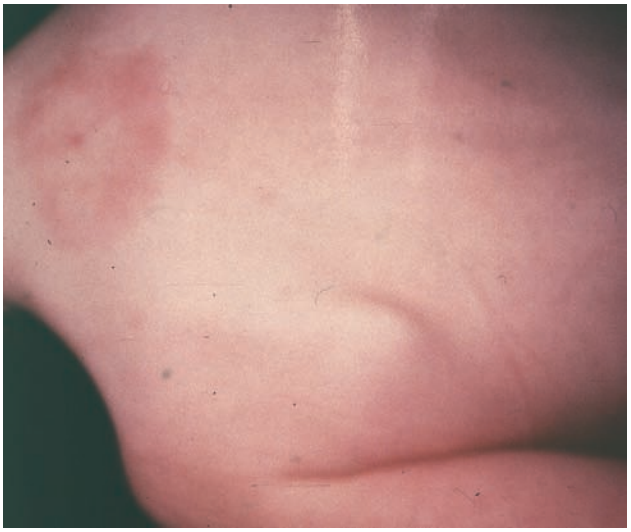


Fig. 35-20. An erythema migrans skin lesion in a patient with Lyme disease.
Photograph: Courtesy of Mary Schmidt, the Armed Forces Institute of Pathology.

presenting as paresthesia and hyperesthesia characterize the chronic involvement of the nervous system.[446] Chronic skin manifestations include Borrelia lymphocytoma and acrodermatitis chronica atrophicans. Chronic arthritis most commonly affects the knee, but this tends to remit spontaneously.

Another manifestation of Lyme disease is post-Lyme syndrome. This is distinct from chronic Lyme disease in that post-Lyme syndrome patients have been treated with antibiotics early in the disease process. Symptoms of severe fatigue, recurrent muscle and joint aches, headaches, mental sluggishness, and difficulty concentrating persist for 6 months or more without response to further antibiotic therapy.[447] These patients are often misdiagnosed as having chronic fatigue syndrome or fibromyalgia. The possibility of *B burgdorferi* persistence in patients with negative serological tests[448] and the presence of *B burgdorferi* DNA in urine of treated patients with symptoms of chronic Lyme disease have been reported.[449] So without a clear-cut definition for Lyme disease, much controversy surrounds the diagnosis and management of this disease. The potential for long-term disability from both chronic Lyme disease and post-Lyme syndrome requires further elucidation of the pathogenesis of this disease.

Diagnostic Approaches

History of exposure is critical to the diagnosis of Lyme disease. A careful history should address issues such as residence in or travel to endemic areas, previous tick exposures, EM lesions, objective or subjective neurologic dysfunction, arthritis, and history of heart disease. Providers may elicit a history of a "summer cold" acquired in an area with endemic Lyme disease. The signs and symptoms of Lyme disease may appear quite specific, but the development of late-stage manifestations may cause diagnostic uncertainty. A careful physical examination, to include a complete skin examination for EM, together with an appropriate exposure history may make the diagnosis. Other skin manifestations, as well as joint, cardiac, and neurological abnormalities, may be detected by physical examination.

Beyond a careful history and physical examination, numerous serologic tests are available to test for antibodies to *B burgdorferi*. An enzyme-linked immunosorbent assay (ELISA) is available to detect IgG and IgM antibodies associated with *B burgdorferi*. The Western immunoblot assay is used to confirm positive and equivocal results from the ELISA, in accordance with the 1999 CDC recommendations.[450] Interpreting these results is not without complications, however; problems include cross-reactivity with normal oral flora and treponema species (eg, *Treponema pallidum*), cross-reactivity with antibodies present in autoimmune diseases such as systemic lupus erythematosus and rheumatoid arthritis, prior exposure to *B burgdorferi*, and the lack of standardization in serologic assays.[434] Serologic tests done at an early stage of Lyme disease may also be negative due to inadequate time for the body to respond with antibodies. Repeat serologic testing is recommended 4 to 6 weeks after the initial test in the early stages of disease. To what extent the availability of new assays (eg, polymerase chain reaction) and genetic sequencing of *Borrelia* species will clarify diagnosis and management of this disease remains to be seen. The diagnosis of Lyme disease still relies on the clinical presentation, the history of exposure, the clinical suspicion of an alert health care provider, and the recognition of the incomplete state of our understanding of this disease.

Recommendations for Therapy and Prevention

Therapy

Prophylactic therapy following a potential bite exposure is not recommended in most circumstances.[451–453] Prompt treatment is indicated for suspected infections.[454,455] For the acute localized illness, doxycycline, amoxicillin, cefuroxime, oral penicillin, and tetracycline have been given for approximately 10 to 20 days with success. The decision of which drug to use is determined by drug allergies, the possibility of co-infection with other tick-borne pathogens, patient compliance, and cost. Misdiagnosis of co-infection with *Babesia microtus*, a malaria-like protozoan, or the *Ehrlichia* species that causes human granulocytic ehrlichiosis may lead to the erroneous diagnosis of treatment-resistant Lyme disease. When co-infections with the human granulocytic ehrlichiosis pathogen are possible, treatment with doxycycline should be considered because it is effective against both infections.[456] Disseminated Lyme disease infection should be treated with intravenous cefotaxime, ceftriaxone, or penicillin for 10 to 30 days[454,455] (Table 35-10).

In patients with continued symptoms following appropriate treatment, use of polymerase chain reaction and culture methods to determine if *B burgdorferi* is present may be considered. Fibromyalgia and chronic fatigue syndrome should also be considered. Other conventional medications may be used

TABLE 35-10

TREATMENT OF LYME DISEASE

Drug	Route	Adult Dose	Child Dose	Duration
Acute Localized				
Amoxicillin	PO	500 mg tid	50 mg/kg/d tid	10-20 d
Cefuroxime	PO	500 mg bid	50 mg/kg/d bid	20 d
Penicillin	PO	250 mg qid	50 mg/kg/d qid	10-20 d
Tetracycline	PO	250 mg qid	Avoid in children	10-20 d
Doxycycline	PO	100 mg bid	Avoid in children	10-20 d
Disseminated and Chronic				
Cefotaxime	IV	2 g qd or q12 h	50 mg/kg/d q12h	10 d
Ceftriaxone	IV	2 g qd or q12 h	50 mg/kg/d	10-14 d
Penicillin	IV	24 million units qd	50,000 units/kg/d	20-30 d

bid twice a day, IV intravenous, po by mouth, q every, qd every day, qid four times a day, tid three times a day
Reprinted with permission from: Gilbert DN, Moellering RC, Sawde MA, eds. *The Sanford Guide to Antimicrobial Therapy*. 31st ed. Hyde Park, Vt: Antimicrobial Therapy, Inc: 2001.

for symptomatic treatment, to include antiinflammatory agents such as aspirin, ibuprofen, hydroxychloroquine, and prednisone. While alternative therapies may be considered, patients should be educated about the dangers of popular remedies such as malariotherapy.[457]

Another complication in the treatment of *B burgdorferi* infection is the Jarisch-Herxheimer reaction, noted in association with antibiotic therapy for spirochetes.[458] After the start of antibiotic treatment, the death of *B burgdorferi* organisms may release large amounts of cytokines and hormones. The minority of patients who experience this reaction feel worse for the first few days, with increased inflammation of EM lesions, fever, and aches, but then improve.

Prevention

Tick populations peak in the spring and summer months, which is when people are outdoors most and opportunities increase for contact between vector and host. The environment surrounding the home is a major determinant of the risk of getting a tick bite; nearly 70% of tick bites are acquired at home,[459] and residences with larger woodlots are more likely to have ticks.[460]

Many environmental controls have been tried to control both the tick and the host populations. Acaricide-impregnated nest material for use by mice has been used to kill the larval stages of the deer tick on the white-footed mouse with mixed results.[461,462] Use of acaricides has successfully controlled the number of deer ticks.[463–466] Removal of deer from proximity to human populations has been used to decrease the numbers of adult deer ticks. These environmental controls are not always successful, however, so the need for personal preventive measures cannot be overemphasized.[467]

The most effective and obvious means of preventing exposure to hard-bodied ticks is to avoid their known habitats, but this is not always possible for military personnel. The risk of Lyme disease can be minimized greatly by the use of the DoD Repellent System (see Chapter 22, Personal Protection Measures Against Arthropods). This system includes wearing a loose-fitting, permethrin-impregnated uniform with pant legs tucked into boots, sleeves rolled down and fastened, and collar closed. Extended-duration DEET lotion should be applied to exposed skin. No repellent system is 100% effective, though, so service members use the "buddy system" to check each other; it works well for finding ticks crawling on the uniform and feeding on the body. Ticks can be found anywhere on the body, but they prefer moist areas.[468] Service members performing buddy checks must be reminded to look for any rash in an area of a tick bite and that such a rash requires immediate medical attention.

The ability of a feeding tick to infect the host is reduced by prompt removal of the tick. Forceps or tweezers should be used to grab the tick as gently

and as close to the skin as possible. The tick should then be slowly and gently pulled away from the bite site until it detaches. Care should be taken not to crush or twist the tick, since this can leave the mouthparts embedded in the skin. Once the tick is removed, it should not be manipulated with bare hands. The tick should be sent in an alcohol-filled container to the US Army Center for Health Promotion and Preventive Medicine, Aberdeen, Maryland, for identification and testing for *B burgdorferi*. The skin should be washed with soap and water, followed by an application of rubbing alcohol. The bite should be observed for at least a month in case a rash or redness develops.[469]

Two vaccines using the outer surface protein of *B burgdorferi* have been developed and tested.[470–472] One that has been approved by the Food and Drug Administration requires a three-shot series (at 0, 1, and 12 months) and has an efficacy of 50% after two doses and 78% after all three doses.[473] While vaccination would decrease the threat that Lyme disease currently presents to military members and their families, personal protective measures still need to be emphasized to prevent Lyme disease if the vaccine fails and to prevent other arthropod-transmitted diseases.

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EHRLICHIOSIS

Introduction and Military Importance

Ehrlichiae have been known as veterinary pathogens since the 1930s. A serious epizootic of canine ehrlichiosis caused the deaths of 200 to 300 military working dogs in Vietnam in the late 1960s. They died of a hemorrhagic disease caused, it was discovered later, by *Ehrlichia canis*.[474] *E sennetsu* (called *Rickettsia sennetsu* until 1984) was described in Japan in the 1950s and was thought to be the only ehrlichial human pathogen. It targets monocytes and causes an illness that resembles mononucleosis.[475–478] *E sennetsu* has been confined to Japan and Southeast Asia.[477,478] It is presumed to be transmitted by ticks, and tetracycline is the treatment of choice.[478] In the last part of the 20th century, two other distinct human diseases caused by ehrlichiae have emerged. Human monocytic ehrlichiosis (HME) has been found to be caused by *Ehrlichia chaffeensis*, which was characterized in 1991. Human granulocytic ehrlichiosis (HGE) is caused by an organism yet to be definitively identified but one that is very similar to *E equi* and *E phagocytophila*, which cause granulocytic infections in sheep, cattle, and horses.[479,480] HGE may be caused by a different strain of one of these two. Although both diseases are caused by ehrlichiae, they have some different qualities. The military has played a role uncovering these two diseases, and the diseases will continue to affect the military, especially because training is often conducted in tick-infested areas.[481] Although there have been many advances in the study of ehrlichiae, much about the organisms and their epidemiology, diagnostics, and control is still unknown. Future control measures should include a system for notifying public health officials of cases and increasing physician and soldier awareness.[482]

Description of the Pathogen

Ehrlichiae are obligate, intracellular, Gram-negative cocci that infect white blood cells.[483] The bacteria can be found grouped into morulae, which are distinct monocytic or granulocytic intracytoplasmic inclusions.[480] *E chaffeensis*, the causative agent of HME, has two identified strains. The first strain, Arkansas, was isolated from a US Army reservist; the second, 91HE17, was discovered in 1995.[479,483] There may be further diversity among the bacteria infecting humans, and the taxonomy will likely become clearer in the future.

Epidemiology

HME and HGE are transmitted by ticks, with greater than 80% of symptomatic people reporting a tick bite within 3 weeks before illness onset.[475,476] Exact incidence rates and prevalence are unknown. Most reported estimates are biased toward identification of the more serious cases.[484]

Human Monocytic Ehrlichiosis

Transmission. HME is believed to be transmitted by *Amblyomma americanum* (the lone star tick) and *Dermacentor variabilis* (the American dog tick).[481,482,485,486] The organism has been found in the white-tailed deer. The presence of persistent bacteremia in dogs suggests that mammals other than deer may be hosts.[481] Disease occurrence is seasonal, with most cases occurring from March to October, and the majority of those in May, June, and July.[477,478,481,486]

Geographic Distribution. Cases have been con-

firmed in 30 states and are concentrated in the south and south-central United States.[484,485]

Incidence. HME seroconversion in a large study of military personnel at Fort Chaffee, Ark, to *E canis* and *E chaffeensis* was 1.3% (13 of 15 positive for *E chaffeensis*). The seroconversion rate was higher in those that actually lived and worked at Fort Chaffee (3.3%) than in those there for training (0.7%).[481] A 12% prevalence was reported among samples submitted for Rocky Mountain spotted fever testing to the Oklahoma State Department of Health.[476] Incidence reportedly rises with age, but older people may be more likely to have worse disease and thus seek medical attention and diagnosis. Median incubation periods have been found to be approximately 7 to 9 days.[484]

Human Granulocytic Ehrlichiosis

Transmission. HGE is transmitted by *Ixodes scapularis* ticks and has also been identified in *D variabilis* ticks.[485,487] Possibilities for a reservoir include deer and rodents. There is year-round occurrence, peaking in June and July,[474,480,482] but tick activity has been found in the upper Midwest in all months of the year except February and September.[487] The median incubation period is 8 days.[482]

Geographic Distribution. HGE has been found in 11 states but more often in the Northeast and Midwest. This is in contrast to HME, which is more often found in the South and South-Central.[474,480] There may also be HGE in Sweden and Switzerland.[482]

Incidence. HGE was discovered in the early 1990s. It was found in 11% of a sample of patients presenting with an undiagnosed acute febrile illness in Minnesota and Wisconsin in the summer and fall of 1993. Annual incidence has been estimated to exceed 50 per 100,000 per year in that location.[487]

Pathogenesis and Clinical Findings

Human Monocytic Ehrlichiosis

In HME, *E chaffeensis* enters the skin via a tick bite and spreads hematogenously. Infection is established intracellularly in macrophages in various tissues. The infection can lead to tissue necrosis, perivascular lymphohistiocytic infiltrates, interstitial pneumonitis, and pulmonary hemorrhage. Granulomas and marrow histiocytosis are a result of the macrophage's reaction to the organism.[482] Much of the pathogenesis and the role of the host in this disease remain unknown.

The extent of asymptomatic infected persons has not yet been fully uncovered. In the study of the military at Fort Chaffee, only 33.3% of seroconverters reported characteristic symptoms.[481] In a study of HME in a retirement community bordering a wildlife preserve, asymptomatic infection with *E chaffeensis* was thought to have occurred because many people with serologic evidence of past infection had not reported illness in the 5 months prior to the study.[486]

Symptoms of those getting medical attention or being studied are nonspecific. Systemic symptoms, such as fever, headache, myalgia, anorexia, and nausea, are common without any clinical diagnostic findings. These clinical findings are similar to those found in Rocky Mountain spotted fever but without the characteristic rash of that seasonal tickborne disease. Complications of HME include serious pulmonary, renal, and cerebral compromise.[477] Hospitalized patients are likely to be older. Laboratory findings, which can be of great assistance in making the diagnosis, include leukopenia, thrombocytopenia, and elevated hepatic transaminases.[477,484] Anemia is common, occurring later in the illness and lasting longer than other hematologic abnormalities.[484] Infiltrates on chest radiographs and cerebrospinal fluid pleocytosis are possible findings amidst complications.[477] A new strain of HME, 91HE77, was isolated from a patient who nearly died and raises the possibility of infection with alternative strains resulting in differential morbidity and mortality.[479]

Human Granulocytic Ehrlichiosis

In HGE, the pathogenesis is unknown after the organism enters via a tick bite. The organism appears to infect myeloid precursors in the marrow instead of mature granulocytes.[482] The corresponding ehrlichiae in animals are believed to somehow impair the host immune response and allow opportunistic infections. Clinical findings in humans include fever, chills, malaise, myalgias, headaches, nausea, vomiting, and rarely a rash.[474,487] The clinical picture is quite similar to infection with *E chaffeensis*, with similar laboratory abnormalities.[474,480]

Diagnostic Approaches

When faced with a patient with possible human ehrlichiosis, serology for both HGE and HME are appropriate because their geographic distributions overlap.[485]

Human Monocytic Ehrlichiosis

E chaffeensis is very rarely isolated from tissue in cases of HME. It is difficult to diagnose early in the course of disease. A high index of suspicion is needed with nonspecific febrile illness, especially when faced with a patient with a history of a tick bite or exposure to ticks.[484] The presence of leukopenia and thrombocytopenia is helpful diagnostically. Diagnosis can be made later after detecting an immune response to *E chaffeensis* antigen or *E canis* antigen. (The *E canis* antigen was used primarily in the early stages of uncovering this organism and is a less-sensitive indicator than finding the *E chaffeensis* antigen.[482]) A 4-fold rise in indirect fluorescent antibody titer of the appropriate level is diagnostic if the clinical picture is consistent.[481,484] Because of the variation in the diagnostic criterion by laboratory, contacting the performing laboratory is useful in determining the minimal peak titer. There is evidence that early treatment and advancing age can result in a decreased serologic antibody response.[481,486] *E chaffeensis*–specific polymerase chain reaction (PCR) is available and can be positive in the absence of antibody criteria for diagnosis. Because of this, PCR is felt to be more sensitive than serologic testing.[482] Unlike the situation with HGE, finding morulae of the organism in the leukocyte in HME is difficult and not a useful diagnostic tool.

Human Granulocytic Ehrlichiosis

The agent in HGE has not yet been isolated, so alternative diagnostic approaches must be used.[480] Peripheral blood smears may be helpful in illustrating neutrophil cytoplasmic morulae of ehrlichiae.[474,480] These morulae are easy to differentiate from other cytoplasmic inclusions.[474] Finding them is the most sensitive and widely available diagnostic tool. Immunofluorescent assay using *E equi* or *E phagocytophila* can be used for serologic diagnosis but not early in the illness.[487] PCR is being refined and is not yet widely available.

Recommendations for Therapy and Control

Therapy

Tetracycline or doxycycline is the treatment for HME and HGE, with typical marked improvement in 48 hours.[474,484,487] Chloramphenicol has been used in some patients who have recovered; the efficacy of chloramphenicol, though, is not clear because some patients respond spontaneously without any treatment, and chloramphenicol is not effective in vitro against *E chaffeensis*. Rifampin is effective in vivo, but clinical experience with this drug is lacking.[488] Improvement with the use of effective therapy can itself be an aid in diagnosis. Treatment must begin before a definitive diagnosis is made because earlier treatment may lower the risk of adverse outcomes.[485] Persistent infection in animals with *E canis* despite treatment has been reported.[478,487] The possibility of persistent infection in humans is still unknown.

Control

People in areas where ticks are common should take precautions. Military personnel should be made aware of the threat of HME and HGE and the fact that they are threats in off-duty environments as well as during field exercises. In endemic areas such as Arkansas, ticks are a threat even for those not engaged in outdoor recreational activities.[477] Precautions include avoiding if possible areas known to be infested with ticks. Routinely using insect repellent and checking for ticks are both important.[485] Tucking trouser legs into boots, blousing trousers, receiving pertinent educational briefings, and using permethrin-impregnated uniforms have been associated with a decreased risk of tick-borne infection.[475,481] These control measures are not practical in the civilian community.[484]

[Kathryn L. Clark]

TYPHUS

Scrub Typhus (*Orientia tsutsugamushi*)

Introduction and Military Relevance

Scrub typhus is an infectious disease that spans a clinical spectrum from mild to fatal depending on the strain of organism, the age and immune status of the host, and the quality of health care provided. While "tropical typhus" has long plagued military forces in Asia and on the Pacific islands, it has only been since the 1930s that scrub and endemic typhus have been distinguished. Because effective antibiotic treatment was not available during World War II, both allied and Japanese forces had large numbers of casualties due to scrub typhus. In some areas, it was a cause of medical casualties second only to malaria. Illustrative of the impact of the infection was the experience of the British in northern Burma: during 2 months in 1944, 18% of one battalion's casualties and 5% of its fatalities were

from scrub typhus.[489]

Scrub typhus remains a major concern for military forces deployed in endemic regions. Reservoirs of infection will continue to cycle in nature, and military operations will place susceptible individuals in exposure situations. Personal protective measures can be effective in reducing exposure, but they require command emphasis to maintain the necessary discipline. This disease, much like malaria, tends to be forgotten by military health professionals between major deployments to endemic regions. Preventive medicine strategies against scrub typhus are an essential part of deployment to Southeast Asia and other endemic areas.

Description of the Pathogen

The etiologic agent of scrub typhus is *Orientia tsutsugamushi*. It is a member of the rickettsial family, which are Gram-negative, obligate intracellular bacteria that multiply in the cytoplasm of infected cells. Because of distinctive characteristics in its outer membrane and rRNA sequence, the organism was reclassified in 1995 from the genus *Rickettsia* into the new genus *Orientia*.[490] Strain variability is greater than that of the other disease-producing rickettsial species. While eight "prototype" antigenic types were defined in 1967, molecular studies now suggest that there are actually more than 60 genetic and antigenic variants unique to different localities. Strains also vary greatly in virulence for both humans and mice (a useful laboratory model).

Epidemiology

Transmission. Scrub typhus is a zoonosis acquired by the bite of infected larval trombiculid mites (chiggers) when humans intrude into an enzootic focus of infection. The natural cycle consists of (*a*) *O tsutsugamushi, (b)* chiggers of the *Leptotrombidium deliense* group (eg, *L deliense, L akamushi, L fletcheri, L arenicola, L pallidum, L pavlovskyi, L chiangraiensis),* and (*c*) small rodents, especially rats of the genus *Rattus*. The mites are both the reservoir and vector of this infection (Figure 35-21). Their larval "chiggers" are the only stage that feeds on humans and rodents (the vertebrate hosts) and usually cause only minimal irritation. The mites ingest lymph and tissue fluids from the subdermis, although their frequently reddish appearance leads to the incorrect impression that they are full of blood. The rickettsial organisms are distributed through all tissues of the mite, including the salivary glands from which they are transmitted during a bite. Transovarial transmission is a necessary part of the maintainence of *O tsutsugamushi* in trombiculid mites. Extensive field observation during World War II indicated that the mites tend to live at ground level rather than on vegetation. Risk of infection to soldiers continuously on the move was associated with their "loitering and resting in contact with the ground en route."[489p186] Certain species of chiggers, though, gather above the ground at the tips of leaves ("lalang" grass) and show that there is diversity in modes of transmission.

Fig. 35-21. *Orientia tsutsugamushi*–infected mite colony established in 1964 at the US Army Medical Research Unit—Kuala Lumpur, Malaysia. The colony was maintained through 62 generations until closure of the Unit in 1989.
US Army photograph.

Geographic Distribution. The geographic distribution of scrub typhus includes eastern and southern Asia and the islands of the southwestern Pacific. Specifically, scrub typhus occurs in Japan, Korea, Tajikistan, the Maritime Territories of eastern Russia, China, Australia, New Zealand, the Philippines, islands in the South Pacific, Indonesia, India, Pakistan, and all of Southeast Asia. It is distributed from sea level to altitudes as high as 7,000 ft (2,100 m) in the Kumaon Hills of India.[489] Within these endemic areas, scrub typhus infection tends to be localized as either well-established or transient "mite islands." Transovarian transmission of the organism provides the mechanism for maintenance of focal endemicity.

There is no such thing as a typical scrub typhus environment. Infected habitats are quite diverse, varying from semideserts, river banks, and sea-

shores to disrupted rain forests and terrain undergoing secondary vegetative growth. Ecological changes that favor the rodents or other small mammals that are the usual hosts of the chiggers occur when stable vegetation is disturbed and allowed to regrow. Military operations and expanding agricultural efforts often produce these types of ecological changes and lead to exposure of service members and rural people to infectious chiggers.[491] Cases of scrub typhus are seen increasingly in nonendemic regions because of intercontinental travel during the incubation period; the nonrecognition of these cases may lead to life-threatening illness.[492]

Incidence. Incidence of scrub typhus varies with geographic location, occupation, and behavior. In temperate areas such as Japan and Taiwan, disease occurrence is seasonal; in warmer areas, seasonal variation may not be detectable. Surprisingly, the seasonal transmission in South Korea and Japan occurs in fall and winter. Disease in indigenous populations is often underdiagnosed. Systematic study of febrile admissions to a central Malaysian hospital in the late 1970s determined that 20% of cases were due to scrub typhus and that this reached nearly 50% in the subgroup of patients who worked in areas where rain forest had been replaced with oil palm groves.[493] Some scrub typhus antibody prevalences in Southeast Asia are 59% in northern Thailand,[494] 21% near Bangkok,[495] 38% in the Pescadores Islands of Taiwan,[496] and 0.8% in Sabah, East Malaysia.[497]

Military personnel deployed to areas endemic for scrub typhus are at high risk of infection and resulting symptomatic disease. Statistics from World War II indicate that more than 7,000 cases occurred in US forces, nearly as many in British and Indian troops, and more than 3,000 in Australian soldiers. Overall incidence figures are unreliable because of clustering of infections in time and place. Risk to military personnel continues to be a problem, as was documented in the mid-1990s in a study[498] that found incidence as high as 15% in Thai soldiers during 4 months of military exercises. Serologic studies in Malaysia[499] and repeated outbreaks among US Marines deployed to the Mt. Fuji region of Japan[500] (Figure 35-22) confirm the continued risk.

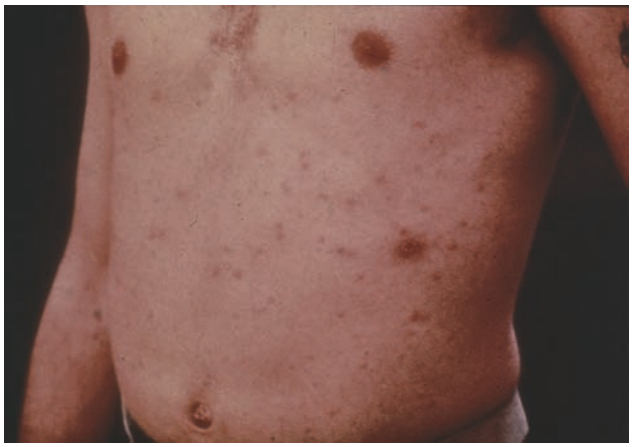

Fig. 35-22. A US Marine with acute scrub typhus acquired while he was deployed to Camp Fuji, Japan, in the autumn of 1983. Note the erythematous (blanching) rash predominately on the trunk and the location of the eschar at the lateral aspect of the right upper quadrant. Photograph: Courtesy of Henry B. Lewandowski, PhD, Savannah, Ga.

Pathogenesis and Clinical Findings

Rickettsiae bind to cellular receptors, are phagocytosed, escape from phagocytic vacuoles into the cytoplasm, and proliferate by binary fission. The organisms exit the host cell either as a mass following host cell lysis or in discrete packets of rickettsiae surrounded by host-cell membrane that buds off from intact cells. Scrub typhus organisms are highly infectious; it is estimated that fewer than 10 viable organisms are an infectious dose for humans. The organisms are transmitted into cutaneous tissues at the site of the chigger's bite. Proliferation in local endothelial cells leads to a visible lesion in about 60% of nonimmune hosts during the 6- to 21-day incubation period. The lesion evolves into an eschar, which is loaded with rickettsiae and highly infectious. Early dissemination via the lymphatic system leads to tender regional lymphadenopathy, which may be augmented by hematogenous spread from infected endothelial cells. Detectable rickettsemia appears late in the incubation period, usually 1 to 2 days before onset of clinical disease.

The wide variation in scrub typhus strains appears to be manifest in its variation in virulence. Symptoms and signs are based on disseminated vasculitis caused by focal infection of the endothelium of small blood vessels. This presents as a maculopapular rash in about one third of patients, which appears late in the first week of illness on the trunk and extremities but may be hard to detect on dark-skinned people. The disease, which may last for weeks, is characterized by fever, headache, and generalized lymphadenopathy. It may be abrupt in onset but is more commonly insidious over several days. Among US Marines in South Vietnam with confirmed diagnoses, the following symptoms and

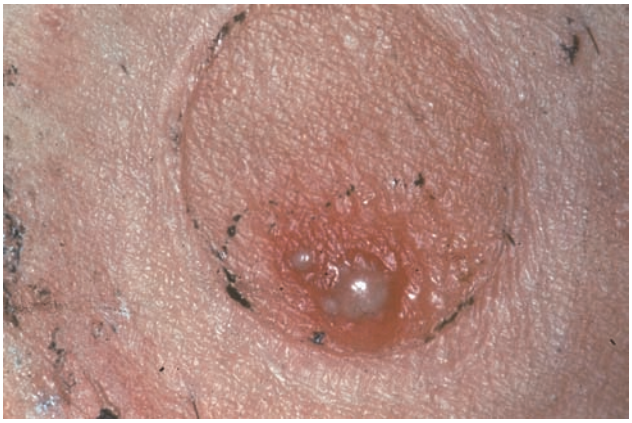

Fig. 35-23. A scrub typhus eschar 1 day after chiggers fed on a US Army volunteer. The chiggers were from the *Leptotrombidium* mite colony shown in Figure 35-21. Photograph: Courtesy of Henry B. Lewandowski, PhD, Savannah, Ga.

signs were observed: eschar (46%), splenomegaly (43%), rash (34%), myalgia (32%), and conjunctivitis (29%)[501] (Figure 35-23). Lung involvement is the most important complication, with adult respiratory distress syndrome the most frequent cause of death. Other complications include deafness, myocarditis, encephalitis, and multiorgan system failure. Mortality rates before the availability of antibiotics ranged from 1% to 55%.[489] Delayed or inappropriate treatment continues to be associated with severe illness and fatality.[492]

Diagnostic Approaches

Clinical. The diagnosis of scrub typhus may be suspected on clinical and epidemiologic grounds. In most parts of Asia, an eschar is pathognomonic of the disease, and a careful search for this lesion in suspected cases is the most important part of the physical exam. Eschars tend to be localized where clothing has been pressed to the skin, as at the ankles and waist. Also helpful diagnostically are rash, conjunctival suffusion, and hearing impairment when associated with onset of illness. Despite these signs, scrub typhus can be easily confused with other febrile illnesses in the endemic area. Prompt, empiric treatment will generally be both diagnostic and curative. Treatment with a tetracycline or chloramphenicol usually leads to clinical improvement and defervescence within 24 to 36 hours.

Laboratory. Rickettsiae may be isolated from the blood of patients, but the techniques are difficult and hazardous. The Weil-Felix test is too insensitive to be useful in diagnosis. Detection of specific antibody is the main tool for proving the diagnosis of scrub typhus. The gold standards for serologic diagnosis are the indirect fluorescent antibody (IFA) and immunoperoxidase (IIP) assays, which use cultured and inactivated organisms as the capture antigen. These antigens have historically been produced and distributed by national research or reference laboratories, but they are now becoming commercially available. Another diagnostic assay in development uses a dot-ELISA (enzyme-linked immunosorbent assay) format. Once validated, such an assay could provide a needed tool for rural clinics and military operations in endemic regions.[502] With any of these serological assays, interpretation of results will differ depending on the population in which it is being used. In adults from endemic areas, acute titers of 1:400 or a 4-fold rise to at least 1:200 may be required to maintain specificity. In contrast, in previously uninfected visitors to an endemic area, a titer of 1:100 would be significant.[503] Molecular assays, under development for scrub typhus and other rickettsial infections, are expected to provide enhanced sensitivity and specificity.

Therapy, Prevention, and Control

Therapy. Tetracyclines and chloramphenicol[504] (Figure 35-24) are specifically effective for the rickettsioses, despite being bacteriostatic (rather than bacteriocidal) agents. Either drug should be given as a loading dose followed by divided daily doses for at least a week and until the patient is afebrile. If treatment is started in the first 3 days of illness, a second course of antibiotics should be given after an interval of 6 days to prevent recrudescence of infection. The responsiveness of scrub typhus to treatment may be changing. In northern Thailand, a high frequency of relapse after treatment associated with relative resistance of *O tsutsugamushi* isolates to both tetracycline and chloramphenicol has been observed.[505] Preliminary studies[506,507] suggest that both azithromycin and rifampin may provide effective alternative therapy for scrub typhus.

Prevention and Control. As general guidance, encampments should not be placed in areas of secondary vegetative growth where agriculture, erosion, or other disturbances favor rodent activity. The best defense for the individual service member against chigger bites is the careful use of treated uniforms and repellents. Three different systems exist for treatment of uniforms with permethrin, which kills chiggers crawling up the uniform be-

a

b

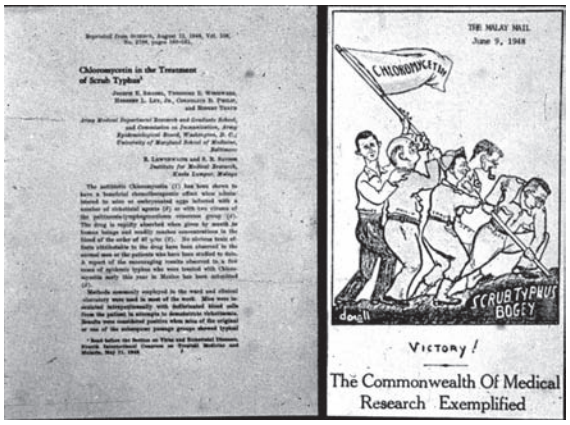

Fig. 35-24. The US Army research team that demonstrated the efficacy of chloramphenicol in the first antibiotic treatment of scrub typhus at the Malayan Institute for Medical Research in Kuala Lumpur in 1948. (a) From left to right, they are: R. Traub, T. Woodward, J. E. Smadel, C. Philip, and H. L. Ley Jr. (b) A cartoon highlighting the accomplishments of the team appeared in the local newspaper, the *Malay Mail*.
(a) Photograph: Courtesy of Dr. Theodore Woodward. (b) The *Malay Mail*

fore they can bite. To be effective, trousers must be bloused inside the boots (not secured with elastic bands) so that the chiggers are forced to crawl up the boot onto the treated uniform before contacting the host.[508] Repellents can be applied directly to exposed skin and, when permethrin-treated uniforms are not available, to boot tops and trouser legs. Two chigger repellents are currently available in the military supply system for topical application to the skin: DEET (N,N-diethylmeta-toluamide) in the standard Army repellent formulation and precipitated sulfur in a specialized formulation for chiggers. When proper permethrin treatment of clothing is not possible, DEET applied from a commercial aerosol can be an effective way of repelling chiggers from boots and trousers. Systemic prophylaxis with weekly doxycycline (200 mg/week) has been demonstrated effective under study conditions,[509] but it has never been used on a routine basis. Weekly administration is necessary so the infected service member develops immunity as the organism multiplies to sufficient levels to induce an immune response. No vaccine is available and development is unlikely because of the diversity of strains.

Old recommendations to treat ground and vegetation with chlorinated hydrocarbons (eg, lindane, dieldrin, chlordane) are no longer appropriate or legal. In fact, no compounds are currently registered for chigger control on an area basis. An alternate approach would be to make an application of a registered insecticide as if for soil pests of turf, though the effectiveness of such treatments is unknown. Burning vegetation will suppress chigger populations for 30 days, but the regrowth can actually foster an increase in vector numbers. Where personnel find themselves in a more stable situation, general rodent control through sanitation, poison baiting, and trapping can limit chiggers and probably suppress transmission of scrub typhus. The most sensitive way to determine whether control or preventive measures are necessary is to test the local human or rodent population for antibodies. Where scrub typhus is prevalent, the resident human population is constantly boosted and maintains detectable antibody, even though no clinical disease is present. Most infected rodents are only mildly affected by scrub typhus but maintain high levels of antibody.

Murine Typhus Fever (*Rickettsia typhi*)

Introduction and Military Relevance

Murine (endemic, flea-borne) typhus is a rickettsial disease caused by the incidental infection of humans with *Rickettsia typhi* transmitted by infected rat fleas. Occurrence of infection depends on proximity to rats, and estimated incidence rates in military groups are not available. During World War II, there were 786 cases with 15 deaths diagnosed in the US Army[510] despite widespread vaccination against epidemic typhus, which provided some degree of cross-protection. Rodent control has been effective in keeping service member exposure low in US military bases, but new missions, such as as-

sistance to refugee groups (which often occupy rodent-infested temporary camps), increase the risk of exposure. Because plague is dependent on the same host (rats) and vector (fleas), the presence of murine typhus in a given setting provides warning that propagation and transmission of that more serious infection is also possible.

Description of the Pathogen

The etiologic agent of murine typhus is *R typhi*, a Gram-negative, obligate intracellular bacterium that multiplies in the cytoplasm of infected cells. It shares group antigens with *R prowazekii*, the cause of epidemic, or louse-borne, typhus. Both of these typhus-group organisms share membrane antigens with *Proteus* and *Legionella* bacilli, the former being the basis of the Weil-Felix reaction against the OX-19 antigen.[511]

Epidemiology

Transmission. Murine typhus is a zoonosis maintained in nature in a cycle involving rats (and to some extent other small mammals such as the opossum) and their fleas, lice, and mites. The rat serves as the reservoir and amplifying host, while the Oriental rat flea (*Xenopsylla cheopis*) and, to a lesser extent, the cat flea *(Ctenocephalides felis)* serve as vectors for transmission to humans.[512] The flea becomes infected by feeding on rickettsemic rats or other small mammals. *R typhi* is then excreted in the feces for the life of the infected flea. Infection of humans occurs by contamination of a flea bite or skin abrasion by the feces of the vector or through inhalation of dried infective feces. The killing of rats may cause their fleas to transfer to humans at an increased rate.

Geographic Distribution. Murine typhus occurs worldwide, depending on human exposure to rodents and their infected fleas. Most important are rats, in particular *Rattus norvegicus* and *R rattus*, which are prevalent in urban and port areas. Dependent on human food and waste, these rats are found around buildings storing food.[513] Rodent infestation of homes is widespread in the tropics, which leads to domestic exposures.[514] Despite the rodent control measures practiced in the United States, continued endemicity of murine typhus is well documented in the warmer states (where many military training bases are located), with hundreds of cases occurring in Texas in the 1980s.[515] Conditions of refugee camps are also conducive to rodent infestation, and murine typhus occurs in them both sporadically and in outbreak form.[516,517]

Incidence. Murine typhus generally occurs sporadically and few incidence data are available. Estimated annual incidence rates among Khmer refugees in two camps in Thailand were 2.2%[517] and 0.5%.[516] Prevalence of *R typhi*–specific antibody varies greatly; in Africa reports show prevalence in the range of 1% to 20%[518]; in Thailand, 7%[519] and 8%[495]; and in Indonesia, 34%.[520]

Pathogenesis and Clinical Findings

The pathogenesis of murine typhus is very similar to that of scrub typhus, with the endothelial cell as the primary target cell. While the basic lesion causing disease is a vasculitis, disseminated rickettsemia is not preceded by the production of an eschar at the site of inoculation. After a 6- to 14-day incubation period, illness begins as fever and severe headache. A maculopapular rash appears on the trunk and extremities several days later but is difficult to detect in dark-skinned persons. Although the untreated disease can be severe, debilitating, and take months for full recovery, complications are few and the case-fatality rate is less than 5% in untreated cases.

Diagnostic Approaches

Clinical. Murine typhus is a persistent febrile illness that lacks specific clinical signs. Less than a third of patients may recall a preceding flea bite or the presence of rodents in their environment.[515] Medical staff are faced with a wide differential diagnosis, which may include malaria, dengue fever, scrub typhus, and mild cases of epidemic typhus. Persistent fever, retro-orbital headache, and rash in an individual with peri-domestic or urban rodent exposure should lead to consideration of murine typhus. Presumptive treatment with a tetracycline or chloramphenicol leads to a favorable clinical response in most patients within 48 hours.

Laboratory. Diagnosis by isolation of the organism from blood is possible but difficult and hazardous. Thus, in practice, laboratory diagnosis depends on serologic techniques. As with scrub typhus, the IFA test is the serologic gold standard. Antigen slides and control sera are commercially available, but fluorescent microscopes are expensive. The still frequently used Weil-Felix test with *Proteus* OX-19 antigen can have a specificity exceeding 95% when the cut-off value for positivity is defined as greater than or equal to 1:160. Unfortunately, at this cut-off, sensitivity is only 80% overall; the assay does not detect antibody in one third of sera collected

during acute infection.[521] A dot-ELISA is commercially available, similar to the one for scrub typhus. This assay is more reproducible than the IFA, has a sensitivity and specificity of about 90%,[521,522] and (similar to the IFA) cannot distinguish murine from epidemic typhus antibodies. The current dot-ELISA requires refrigeration of reagents, but efforts are underway through lyophilization to remove this limitation to field deployability.

Therapy, Prevention, and Control

Treatment regimens are the same as for scrub typhus (see above). The basis of prevention of murine typhus is domestic rodent control directed at the Norway rat (*R norvegicus*) and the roof rat (*R rattus*). Good rodent control can be achieved by preventing access of rodents to buildings, practicing good sanitation, poison baiting, and trapping. Once an infestation of rodents occurs, it is important to protect people from existing flea populations before starting rodent control. The usual recommendation is to dust burrows (Norway rats only) and runs with carbaryl dust, but indoor flea treatments with pyrethroids would also be helpful. For individual service members, DEET in the standard Department of Defense repellent is effective against fleas. Where available, commercial aerosol repellents applied to the trousers and boots are convenient and will prevent flea bites when personnel pass through infested buildings or bunkers. Antibody assay of local domestic rodents would probably be the most sensitive indicator of the presence of murine typhus.

Epidemic Typhus Fever *(Rickettsia prowazekii)*

Introduction and Military Relevance

Epidemic typhus is a louse-borne rickettsial disease with significant mortality that tends to be associated with the poor hygiene frequently accompanying war and civil dislocations. During World War I, epidemic typhus killed 150,000 people in Serbia, including 50,000 prisoners of war and one third of the country's physicians.[510] During World War II, the threat of typhus led the US Secretary of War to establish the Typhus Commission. Because of the Commission's recommendations and research, advances were made in diagnostics, therapeutics, louse-control methods, and vaccine development (Figure 35-25). A military-wide program of vaccination and command enforcement of Commission recommendations led to the occurrence of only 104 cases of epidemic typhus in the US Army during World War II, despite epidemic occurrence in other military and civilian populations.[510] There was no significant incidence of epidemic typhus in the US military during either the Korean or Vietnam wars. In contrast, immediately following World War II more than 30,000 cases were reported in Japan and Korea, with a 6% to 10% mortality rate in both countries.[523] Newer missions, including disaster and humanitarian relief efforts that entail medical care of displaced and refugee populations, are likely to place medical units at risk of infection.

Fig. 35-25. Epidemic typhus prevention during World War II. US Army Medical Service personnel at the Mediterranean Base Section in Algiers treat Arab children with new insecticide powder (DDT) designed to kill typhus lice. Photograph: Courtesy of Dr. Theodore Woodward.

Description of the Pathogen

The etiologic agent of epidemic typhus is *R prowazekii,* a Gram-negative, obligate intracellular bacterium that multiplies in the cytoplasm of infected cells. It shares group antigens with *R typhi*. Both typhus group rickettsiae have epitopes also found on the membranes of *Proteus* (OX-19) and *Legionella* bacilli.[511] The epitopes produce cross-reactions.

Epidemiology

Transmission. Humans are infected by *R prowazekii*–containing feces of the body louse (*Pediculus humanus*), which is distinct from the head louse. Body lice actually live and lay eggs in clothing, exiting at least daily to take blood from the host. In-

fection usually occurs by rubbing the crushed body or feces of the louse into its bite or into skin abrasions but may also occur by inhalation or exposure of mucous membranes. Humans act as the reservoir and maintain the infection between epidemics. Lice may become infected from patients with either acute or recrudescent typhus. *R prowazekii* can remain infectious for months in dried louse feces. In the United States, a zoonosis also exists in flying squirrels and the organism is occasionally spread to humans, most likely via the squirrel flea.

Geographic Distribution. Epidemic typhus occurs in colder climates where people live in conditions of poor hygiene leading to infestation by body lice. Endemic foci exist in the mountainous regions of Mexico and Guatemala, the Andes mountains in South America, the Himalayan countries (eg, Pakistan, Afghanistan), the highland region of Africa (eg, Ethiopia, Burundi, Rwanda, Lesotho) and northern China. The Balkans, Eastern Europe, and Russia continue to experience high rates of recrudescence (Brill-Zinsser disease) because of the millions of people infected during World War II.

Incidence. Epidemic typhus is usually associated with war, famine, and social disruption, which predispose to lousiness and increased population density. An example of this is the major outbreak during the war in Burundi in 1996 and 1997.[524] Endemic patterns of disease occur, such as the sporadic cases seen in the Andes, and are spread at low rates from either acute or recrudescent cases.

Pathogenesis and Clinical Findings

Epidemic typhus occurs after an incubation period of 8 to 12 days following exposure to the organism and is characterized by rickettsemia and systemic infection of endothelial cells. The disease is more severe than scrub or endemic typhus, with fatality rates of 10% to 60% in untreated patients. If the patient does not die in 14 to 18 days, he or she usually recovers, with defervescense over a 2- to 4-day period.

Diagnostic Approaches

Clinical. In the appropriate epidemiologic setting, louse-borne typhus should be suspected in patients with abrupt onset of persistent fever (39°C-41°C), intractable headache, and relative bradycardia. No eschar develops. A rash occurs after 4 to 7 days, starting on the trunk and spreading to the extremities. Multiple systems are involved; death is associated with stupor, renal failure, and hypotensive shock.

Laboratory. The Weil-Felix agglutination test with *Proteus* OX-19 antigen is available and quite specific. IFA can be used to diagnose typhus but requires specific preabsorption to allow differentiation from murine typhus. Differentiation can also be made by species-specific complement fixation or toxin neutralization tests. *R prowazekii* can be isolated from blood or tissue by inoculation of tissue culture or guinea pigs. This is useful to prove etiology but is too slow for use in diagnosis of the individual patient.

Therapy, Prevention, and Control

Therapy. A single dose of doxycycline (100 or 200 mg) is the treatment of choice for epidemic typhus. Temperature usually normalizes in about 60 hours. Recrudescence, which is usually mild, may occur within months of initial infection or many years later (Brill-Zinsser disease); it should be treated with another course of the therapy. Supportive therapy and antibiotics for complicating infections may be required.

Prevention and Control. Medical personnel dealing with lousy prisoners of war or refugees are at considerable risk of infection by inhalation of louse feces and body parts during initial processing of these individuals. A simple particle filter paper mask probably minimizes risk until prisoners or refugees can be bathed and treated for lice. Personnel should also practice good hygiene by bathing after coming in contact with lousy people. The permethrin-treated battle dress uniform should prevent infestation of service members, but this has never been tested. Lice can be eliminated from clothing by boiling or dry cleaning and from individual people by application of pediculicides, but these techniques require a great deal of attention for each lousy person. Formerly, the US military had a system for quickly delousing people using a power duster to inject insecticidal powder into the clothes currently worn by a person. That system depended on an insecticide (lindane) that is no longer considered safe and on equipment that is no longer maintained. There is some possibility that ivermectin could be used as a systemic pediculicide and so eliminate the need for dusting lousy individuals, but this use of the drug has not yet been tested. Long-term control depends on improved hygiene and living conditions. When intensive exposure is anticipated, doxycycline may be used for prophylaxis (100 mg 1 or 2 times per week) although its

efficacy has not been proven. Vaccines, consisting of either killed or attenuated organisms or of purified subunit proteins, have been developed and tested but are not currently available except in Russia. Noteworthy is the fact that murine typhus provides cross-immunity against epidemic typhus.[525]

Spotted Fever

Introduction and Military Relevance

Human diseases caused by spotted fever group (SFG) rickettsiae, while having wide geographic distribution, occur infrequently. The diseases and their etiologic agents include the ixodid tick-borne diseases Rocky Mountain spotted fever (RMSF) (*R rickettsii*), Mediterranean spotted fever (MSF) (other names: boutonneuse fever, Kenya tick typhus, Indian tick typhus, Marseilles fever) (*R conorii*), South African tick typhus (*R africae*), North Asian or Siberian tick typhus (*R sibirica*), Japanese spotted fever (*R japonica*), Queensland tick typhus (*R australis*), and Flinders Island agent *(R honei*). Unlike their status as the reservoir of epidemic typhus–causing *R prowazekii*, humans are incidental hosts of SFG rickettsiae and become infected through the bite of infected ticks or mites that normally feed on a variety of small mammals. RMSF is the most severe of the SFG rickettsial diseases and is the most common fatal tick-borne disease in the United States. RMSF was first recognized in 1873 in the Bitter Root Valley of western Montana. Incidence has declined in that region since the 1930s while increasing in the eastern United States, where it had previously been uncommon.

Studies in military populations have documented the episodic impact of SFG rickettsioses on military training and operations in tick-infested areas.[526] During World War II, the first isolates of *R australis* were recovered from the blood of two soldiers deployed in North Queensland, Australia.[527] In 1989, a cluster of tick-borne infections due to *R rickettsii* or *Ehrlichia* species or both occurred in two military installations in the continental United States.[528] Following a 2-week deployment to Botswana in 1992, 31 of 169 US airborne soldiers based at Vicenza, Italy, were diagnosed with laboratory-confirmed spotted fever rickettsiosis consistent with African tick-bite fever.[529] Later that year, during Operation Restore Hope, MSF was diagnosed in a 36-year-old male soldier following deployment to Somalia.[530] Thus, while SFG rickettsioses continue to occur in service members, the impact of these diseases on military operations and readiness is quite limited.

Description of the Pathogen

The organisms that cause these diseases are Gram-negative, obligate intracellular bacteria that multiply in the cytoplasm of infected cells. In addition to the intracytoplasmic growth common to rickettsiae, the SFG organisms also grow within the nucleus in a small proportion of cells. They have common protein and lipopolysaccharide group antigens and some proteins distinguishable by Western blot. Polymerase chain reaction/restriction fragment length polymorphism (PCR/RFLP) analyses are most useful for identifying and distinguishing species.

Epidemiology

Transmission. Etiologic agents of the rickettsial spotted fevers are enzootic in nature. Several species of ixodid ticks function as reservoir, host, and vector. The agents are transmitted both vertically through transovarial passage and horizontally through vertebrate hosts of the ticks. In the eastern United States, the dog tick (*Dermacentor variabilis*) is the most common vector of *R rickettsii;* in the west it is the wood tick (*D andersoni*). *Amblyomma cajennense* is the common vector in Central and South America. *Rhipicephalus sanguineus* is the most common vector of *R conorii* in Europe, Asia, and northern Africa; in east and southern Africa, *Haemaphysalis* (spreading *R conorii*) and *Amblyomma* (spreading *R africae*) ticks have been implicated. *D nutallii* (spreading *R sibirica*) and *Ixodes holocyclus* (spreading *R australis*) are also vectors.

Geographic Distribution. In the United States, the vast majority of cases of RMSF are reported in the southeastern states, particularly North and South Carolina, but cases are reported in nearly all states.[531] *R rickettsii* is distributed throughout the Western hemisphere; *R conorii* in Africa and the Mediterranean littoral including France, Italy, and Spain; *R australis* in Australia; *R japonica* in Japan; and *R sibirica* in Asia and Eurasia. New distributions are likely to occur; spotted fever was described in both Japan and Thailand for the first time in the 1990s.[532,533]

Incidence. The incidence of RMSF in the United States increased through the 1960s and 1970s to a high of 1,192 cases in 1981, then declined steadily to about half that number in 1995.[534] Recent incidences have been highest in Oklahoma, the Carolinas, and Tennessee, with these states accounting for half of all reported cases.[531] Ninety percent of cases occurred between April and September, with half presenting in May and June. There were 242 cases

of RMSF in the United States between 1981 and 1992, 4% of which were fatal; however, in a Brazilian outbreak in 1990-1991, four of six cases were fatal.[535] The fatality rate for MSF has been reported at 2.5%.[536]

Pathogenesis and Clinical Findings

Pathogenesis of the SFG rickettsiae is similar to that of the scrub typhus group and typhus groups, with endothelial cells, including those of capillaries, being the primary target. The bite of the arthropod vector (in the case of ticks, the tick can remain attached for several hours) results in the inoculation of rickettsiae directly into the dermis. Infection by scarification of tick feces and inoculation of conjunctiva by crushed tick juices have been reported. The incubation period for RMSF is 2 to 14 days (mean of 7 days)[531] and about 20% of patients have a small primary lesion. The disease is characterized by fever (in 94% of patients), severe headache (86%), myalgia (82%), rash (80%), malaise, nausea, vomiting, and abdominal pain. The rash appears on about the third day of illness and is pink and maculopapular, localized to the forearms, palms, soles, and legs. In MSF, the frequency of rash is nearly 100% and an initial cutaneous lesion with a necrotic center ("tache noire") at the site of tick bite is frequent[536] (Figure 35-26). The disease course of MSF, Oriental spotted fever, and African, Siberian, and Queensland tick typhus tends to be milder than that of Israeli MSF, which is itself milder than that of RMSF.

Diagnostic Approaches

Clinical. Only about half of confirmed cases of RMSF have the classic triad of rash, fever, and headache.[531] Absence of a rash ("spotless fever") or having G6PD deficiency is associated with increased severity. RMSF should be suspected in patients exposed to wooded areas from April to October or with a specific history of tick bite.

Laboratory. The IFA test remains the standard serological test for the SFG rickettsiae and is highly group specific and group sensitive. Four-fold rises in IgG to greater than 1:64 are considered to be diagnostic, whereas single serum titers greater than 1:128 are suggestive. For MSF, a 4-fold rise or a single titer greater than 1:80 in conjunction with presence of two of the three signs of fever, rash, and eschar is considered diagnostic.[536] Antigen slides for IFA and dipstick assays for detection of *R rickettsii* and *R conorii* are available commercially. The agents can be identified *in situ* by direct fluorescent antibody staining of frozen sections of biopsied lesions. The test is highly specific; however, a sensitivity of about 70% means that a negative test does not rule out infection. Polymerase chain reaction was used to diagnose SFG rickettsiosis in a soldier whose biopsy was negative by direct fluorescent antibody.[530]

Therapy, Prevention, and Control

Therapy. Empiric treatment should be initiated before laboratory confirmation (tetracycline: 25 mg/

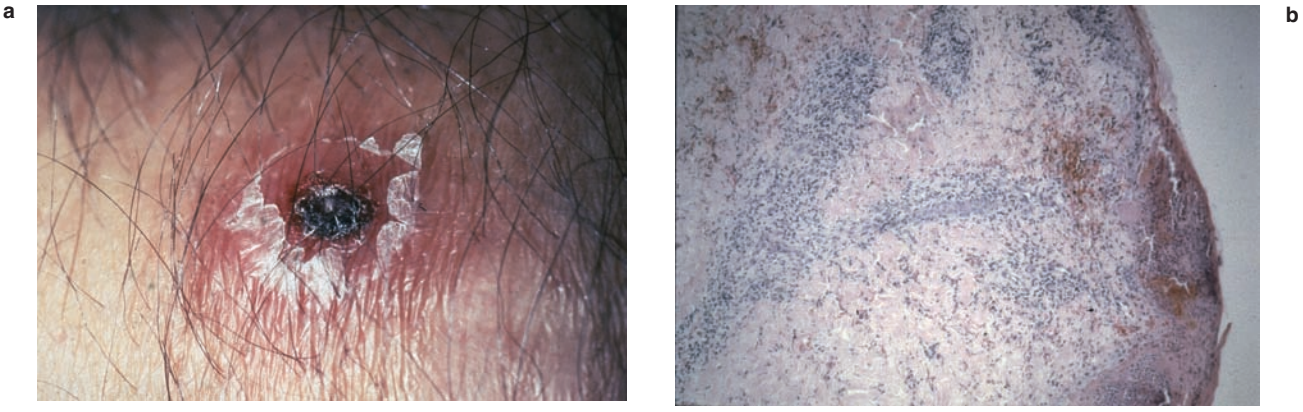

Fig. 35-26. (a) An eschar or "tache noire" on the right calf of a soldier who acquired *Rickettsia conorii* infection in Somalia in 1993. Note the centralized necrosis within the lesion. (b) A hematoxylin and eosin stain of biopsied section (x140) from the eschar in (a). Note the necrosis of the epidermis and the superficial dermis and the perivascular lymphohistiocytic infiltrate with endothelial cell swelling.
Reprinted with permission from: Williams WJ, Radulovic S, Dasch GA, et al. Identification of *Rickettsia conorii* infection by polymerase chain reaction in a soldier returning from Somalia. *Clin Infect Dis.* 1994;19:93–99.

kg per d in four divided doses, doxycycline: 200 mg/d in two divided doses, or chloramphenicol: 50 mg/kg per d in four divided doses).

Prevention and Control. Ticks are often concentrated at the edges of roads, along paths created by large mammals, and near places where animals get water. The permethrin-treated battle dress uniform offers excellent protection from ticks. DEET in the standard DoD repellent discourages tick bites. DEET applied to the trousers and boot tops repels ticks crawling up the outer clothing to find a place to bite. Blousing trousers inside the boots provides more protection than using elastic bands. Area treatment with pesticides for ticks is effective, especially at encampments, fighting positions, and along paths. In infested areas, service members should check themselves for attached ticks at least twice a day, examining all areas including the groin, perineum, and hairline. Whenever possible, ticks should be removed with a forceps, grasping the tick as close to the skin as possible and pulling with a steady, increasing tension. A fully attached tick can sometimes be dislodged more easily if a sterile needle is used to loosen the mouthparts, probing their ventral side while pulling with forceps. All skin contact with the tick should be avoided to prevent exposure to infectious hemolymph (tick blood released from a crushed tick) or coxal fluid (a clear liquid released from glands between the legs during feeding). Where ticks are particularly abundant, it can be useful to keep a small container of alcohol for disposal of ticks. Surveillance of ticks can be accomplished with tick drags (pieces of cloth trailed through the area of interest) or carbon dioxide released from dry ice on a white cloth. No licensed vaccine is presently available.

[Arthur E. Brown, Daniel A. Strickman, Daryl J. Kelly]

PLAGUE

Introduction and Military History

Plague is one of the most deadly infectious diseases in history and has been a "traditional scourge of military operations,"[537p8] often "brought in the train of armies or of commerce."[538p167] The disruption and devastation that occur in the wake of a war lead to a breakdown in sanitary conditions, to crowding, and consequently to favorable conditions for the proliferation of rats and fleas. Despite the expansion of medical knowledge in the 20th century, humans have not been able to eradicate the disease, as is evidenced by a succession of outbreaks and the persistence of natural foci.[538]

In addition to its potential to cause substantial mortality, plague can have a tremendous psychological impact, as is described by Cartwright: "The Black Death must have seemed to be of supernatural origin, a punishment inflicted by a higher power upon unknown sinners for unknown crimes."[539p46] In 1994, an outbreak of pneumonia with a high fatality rate in India was perceived as a global health emergency[540] and caused heightened awareness and increased surveillance internationally.[541] There were press reports at the time describing an exodus of hundreds of thousands of people from the city of Surat, where the outbreak began. The cost of implementing emergency response systems internationally and the losses in Indian tourism were substantial.[542] A few cases were later confirmed as plague but by unvalidated serologic techniques. The devastating psychological and economic consequences of the Indian experience, however, illustrate the importance of using microbiological confirmation and a thorough assessment of risks by a multidisciplinary team before declaring an epidemic emergency.[540,543]

The first documented plague epidemic may have been the Bible's description of illness among the Philistines in 1320 BC.[538,539,544] Since then, there have been three pandemics, all related in part to military operations. The first was the Justinian plague of the 6th century, named after the Byzantine emperor at the time. The outbreak began in Egypt and spread throughout Asia Minor, Africa, and Europe via merchant and military travel. In Constantinople, the epidemic affected the city for 4 months, with 5,000 to 10,000 people dying each day during peak periods. Many of the city's services were disrupted, including the food supply.[545] Warnefried, a German monk and historian from the 8th century, chronicled the devastation made by the disease, which "depopulated towns, turned the country into a desert, and made habitations of men to become the haunts of wild beasts."[544p12] The second, and most well-known, pandemic began its spread to Europe in Caffa, on the Black Sea, in 1346. It has been alleged that the outbreak within the city walls began after Tartar armies besieging the city began catapulting plague-infected corpses into the city. Individuals fleeing the area and merchant ships were suspected of carrying the infection to Europe, beginning a series of epidemics throughout the continent that

killed up to one fourth of the population[546] and became known as the "black death."[538] Before devastating Europe, the disease had already killed 250 million Asians.[545] The third pandemic occurred from 1894 to 1920 and may continue today.[540] It began when Chinese troops were sent to the Yunnan Province, a plague-endemic area, to quell a Muslim rebellion. The disease subsequently spread—via a series of outbreaks that followed the military's movements to the coastal cities and beyond—to surrounding Asian countries.[538] During World War II, there were numerous reports of outbreaks in North Africa and the China-Burma-India theater among the civilian population in endemic regions. DDT was used for flea control along with other measures, including rodent trapping, poisoning, and gassing; community sanitation; spraying of ships and aircraft for insect vectors; inspection and quarantining of cases; and restricting access to high-risk areas.[547] During the Vietnam War, although the country was widely known to be endemic for plague and service members were definitely exposed to rat fleas (as was shown by 58 cases of murine typhus), US vaccination efforts may have been the reason there were only eight recognized cases among US forces.[537,548] The US military has not had a severe problem from the disease, largely due to the implementation of effective control measures. Respect for this disease is warranted, though, because an army could be incapacitated quickly by an outbreak of pneumonic plague.

Because of the devastation it can cause, plague is a potential biological warfare agent.[549] During World War II, the Japanese conducted biological warfare experiments on Chinese prisoners, exposing them to plague and other agents. The Japanese also released rice and wheat with plague-infected fleas over Chuhsien and Ningpo in China, killing 21 and 99 people, respectively.[550] During the Korean War, there were unsubstantiated allegations that US planes scattered plague- and cholera-infected insects.[550,551]

Although service members can be at risk for plague when engaged in combat or during operations involving disasters, refugees, or humanitarian assistance, they may also be at risk during routine training exercises in the United States. Plague has been detected in rodents on or around military installations in California, Arizona, Colorado, New Mexico, Washington, Oregon, Texas, and Utah.[552] A case of bubonic plague in a soldier was reported in 1992 after the soldier had been in central California on a military exercise.[553]

Description of the Pathogen

Plague is caused by infection with the Gram-negative, nonspore-forming, nonmotile coccobacillus *Yersinia pseudotuberculosis* subspecies *pestis*, commonly known as *Y pestis* and previously known as *Pasteurella pestis*.[538,554] It was first isolated and described in 1894 by Kitsato and Yersin while both were studying an outbreak of bubonic plague in Hong Kong.[538] Controversy still exists over which one should properly receive credit for discovery of the organism.[546]

Epidemiology

Transmission

Plague is primarily a zoonotic disease of wild rodents[538] and is typically transmitted among them or to other animals (including domestic animals) or humans by the bite of infected fleas infesting the animals. In addition to vector-borne transmission, plague can be transmitted by infected body fluids and tissues through cuts and abrasions. Transmission by ingestion of infected tissues by carnivores has been demonstrated[546] and could theoretically occur in those who ingest uncooked or undercooked rodent meat. Infection can also occur by mechanical spread of airborne organisms through ocular and oropharyngeal mucous membranes. Direct spread to the lungs by infectious droplet nuclei from a human or animal with pneumonic or pharyngeal plague also occurs.[554] Asymptomatic individuals with culture-proven pharyngeal plague have been noted,[546,555] but their role in the transmission of human infections is not known.

Except in the case of pneumonic plague, humans are both accidental and dead-end hosts and do not play a role in the maintenance of *Y pestis* in nature. The risk of transmission to humans corresponds to the presence of the flea vector because plague is generally transmitted to humans by the bite of an infected flea. The largest outbreaks in humans have had the common black and brown rats as reservoirs (*Rattus rattus* and *Rattus norvegicus*, respectively) and the oriental rat flea (*Xenopsylla cheopis*) as the vector.[546] In the United States, only sporadic cases of human plague occur and are generally associated with sylvatic foci and reservoirs such as the ground squirrel, rock squirrel, and prairie dog.[556] Large-scale human outbreaks can occur, however, if humans live in overcrowded, unsanitary urban conditions near a large infected commensal or wild

rodent population. Plague is generally felt to occur when humans enter the areas of rodent habitat while an epizootic is ongoing, but infected animals may enter areas of human habitat as well.[557] This includes domestic dogs and cats, which may carry infected fleas into homes.[62p381–387] Since 1977, cats have played an important role in transmitting plague, including pneumonic plague, to humans in the United States.[558]

Geographic Distribution

In recent years, plague has been reported on the major continental areas of North and South America, Africa, and Asia.

Incidence

Data on worldwide incidence are crude and incomplete. In addition, no uniform criteria exist for defining a confirmed or suspected case.[546] For the period 1978 through 1993, there were 16,921 cases and 1,642 (9.7%) deaths reported worldwide (average of 1,057 cases per year, range of 200 to 1,966 per year). During the period 1978 through 1992, the six countries that reported human plague nearly every year were Brazil, Madagascar, Burma, the United Republic of Tanzania, the United States, and Vietnam. China has reported cases annually since 1985. From 1983 through 1992, 61% of cases and 77% of deaths occurred in Africa.[559]

Plague has exhibited a seasonal incidence. In the United States between 1950 and 1975, 84% of cases related to exposure to wild animals and their fleas occurred between May and September. In Brazil, October to December is the peak time. The fluctuations may be related either to seasons when people spend more time outdoors either for leisure or working during the harvest or to variations in reservoir populations. The seasonal variation may also be related to characteristics of the flea vector. The life span of *X cheopis* is 27 days once its feeding tube is blocked by the plague bacillus; however, the fleas will die rapidly if the temperature rises or the humidity falls. In addition, coagulation of the ingested blood in the alimentary tract of the flea is felt to be important in the disease cycle and does not occur at temperatures greater than 25°C.[546]

From 1944 through 1993, there were 362 reported human plague cases in the United States, with the majority occurring in New Mexico, California, Colorado, and Arizona. Human plague has now been reported from all states in the western continental United States, and epizootic plague appears to be spreading eastward and northward.[540,558] In 1993, there were 10 confirmed cases: seven bubonic, two primary septicemic, and one pneumonic. There was one death. Recent trends include peri-domestic transmission, with cats as a source of human infection[558] and increased risk of human infection because of urban spread into previously wild areas.[552]

Pathogenesis and Clinical Findings

After the flea ingests a blood meal from an animal with *Y pestis* bacteremia, a coagulase from the bacilli clots the blood in the flea's foregut, thus blocking its ability to swallow. The organism multiplies in the clotted blood. During subsequent feeding attempts, thousands of organisms may be regurgitated by the flea into a person's skin. Once in the skin, the bacteria travel through lymphatic channels to regional lymph nodes. Host mononuclear phagocytes and polymorphonuclear leukocytes phagocytize the bacilli, which have a small amount of envelope antigen. The bacilli are not destroyed but may multiply in the mononuclear phagocytes and become relatively resistant to more phagocytosis once the mononuclear cell lyses. Infected lymph nodes are notable for concentations of extracellular bacilli and polymorphonuclear leukocytes, as well as destruction of the normal lymph node architecture and hemorrhagic necrosis. Explosive multiplication of the organisms occurs with transient bacteria. In the absence of therapy, intense and destructive inflammatory reactions occur in many organs, especially the lymph nodes, liver, and spleen. Explosive bacterial growth generally precedes death.[546,560]

Cases of plague are categorized as bubonic, septicemic, and pneumonic, although other more benign forms have been recognized.

Bubonic Plague

A patient with bubonic plague typically will have the acute onset of fever, malaise, headache, and diffuse aches from 1 to 7 days after being bitten by an infected flea. This may be followed by nausea and vomiting several hours later,[62,538] although vaccination may reduce the incidence and severity of disease.[561] Localized pain and tenderness will occur before palpable adenitis. Buboes are characteristic of the disease but not pathognomonic and usually involve a single lymph node chain in the groin, axilla, or neck. The infecting bite usually occurs on the lower extremity, hence the femoral nodes are the nodes affected up to 90% of the time.[538,553] The bubo can be so tender that patients attempt to avoid any movement of the affected area.[544,556] A striking

feature of bubonic plague is the sudden onset of the fever with a bubo, the rapid development of intense inflammation in the bubo, and the fulminant course that can produce death as quickly as 2 to 4 days after the onset of symptoms.[556] The mortality from bubonic plague in treated individuals is 2% but as high as 50% to 60% in the untreated.[562,563]

Patients with bubonic plague may have a variety of dermatologic findings. Up to one fourth of patients in Vietnam had pustules, vesicles, eschars, or papules near the bubo or anatomic area drained by the affected lymph nodes. Rarely, these lesions can progress to cellulitis or abscesses; they may even ulcerate, yielding a large carbuncle.[555,556] A small vesicle (which may go unnoticed) or carbuncles can develop at the primary site of infection, or secondary carbuncles or necrotic ulcers of hematogenous origin may develop on all parts of the body. Generalized pustular eruptions, known as plague pox or plague variola, have been recorded. The dermatologic findings may coincide with or precede the formation of the buboes.[544] Plague meningitis is a complication that can occur when the meninges are hematogenously seeded from a bubo, often after bubonic plague has been inadequately treated.

Septicemic Plague

Septicemic plague can be secondary to untreated bubonic plague or it can be primary, in the absence of adenopathy. Dissemination to any organ can occur, but the most common sites are the lungs, eyes, meninges, joints, and skin. Small vessels can be occluded secondary to vasculitis, leading to purpura and even gangrene of the skin and digits. These obvious physical examination findings probably are responsible for the term "black death."[554] Septicemic plague is rapidly fatal if untreated.

Pneumonic Plague

Plague may affect the lungs in several forms, which exist along a continuum: well-marked foci with consolidation, congestion and edema without consolidation, or a transitory form with a slight pneumonitis.[538,544] The first of these three types is classic pneumonic plague. The patient does not develop a bubo but within 24 hours of the onset of symptoms develops a cough with mucopurulent sputum, which may progress to sanguinopurulent sputum.[538] Although the patient appears acutely ill, it may take 6 to 8 hours for definite signs of clinical pneumonitis to appear. Chest x-ray evidence of pulmonary infiltration can be present despite the initial lack of physical signs of pneumonia.[544,564]

Secondary pneumonic plague occurs in persons with bubonic or septicemic plague when the lungs are seeded by organisms in the bloodstream. In patients with secondary pneumonic plague, average survival time ranges between 2 and 4 days.[553] Primary pneumonic plague occurs from the inhalation of infectious droplet nuclei expelled from a person or animal with pneumonic plague. The average survival time for those with primary pneumonic plague is 1.8 days.[562] The public health consequences of pneumonic plague can be serious[554] because it has a short incubation period of 2 to 4 days, is rapidly fatal, and spreads rapidly to close contacts. An outbreak of pneumonic plague could literally halt an army unit in its tracks.

Plague pharyngitis is a rare form of the disease that may occur as a result of inhalation of organisms from patients with pneumonic plague or from ingestion of plague organisms. Patients with plague pharyngitis may have anterior cervical lymph node swelling and tonsillar exudates, although asymptomatic forms have been noted.[546,555]

Other

More benign forms of plague have been noted. In the type called "ambulant" plague, a vesicle forms at the site of skin inoculation and there is mild local lymphangitis without systemic signs. A second type, called "pestis minor," may have a variable presentation and is difficult to distinguish from cases of bubonic plague without significant bacteria. One or more lymph nodes may be involved, but there is not the significant pain associated with bubonic plague. The patient may have some systemic complaints of fever, headache, and prostration, but the complaints do not last longer than a week and do not include the marked local inflammation of bubonic plague.[544] Pestis minor occurs more commonly at the beginning and end of outbreaks and has been postulated to be related to subinfective doses of *Y pestis*, probably transmitted by flea bites, immunizing the population. Asymptomatic forms of plague exist, since individuals without clinical illness have had plague cultured from the throat despite either antibiotic treatment or vaccination.[555] Whether these "carriers" are contagious is not known.

Diagnostic Approaches

Plague can lead to death in a matter of hours to days in 60% to 90% of patients if they are untreated.[538] Early recognition is key to survival, especially in patients with pneumonic or septicemic

plague. Risk for fatality has been linked to a delay in proper diagnosis and treatment.[558] The first step in diagnosis must be a high index of suspicion in a febrile patient who lives in or has recently visited an endemic area. Suspicion should be heightened if the patient recalls contact with fleas or direct contact with wild animals or the physical examination demonstrates a painful bubo, a cough, or meningeal signs (Figure 35-27). Patients are typically febrile with a tachycardia and may be hypotensive secondary to vasodilation. In addition, physical examination may also demonstrate a palpable and tender liver and spleen.[556] The leukocyte count is typically but not necessarily elevated (even up to 50,000/mm^3).[538]

Plague may present in an atypical manner, leading to delay in diagnosis and death. Crook and Tempest,[565] in a review of 27 cases seen at an Indian hospital in New Mexico from 1965 through 1989 categorized plague patients into five clinical presentations: (1) classic bubonic plague, (2) fever, sore throat, and headache, (3) nonspecific febrile syndrome, (4) fever with urinary or gastrointestinal symptoms, and (5) fever with meningeal signs. Six out of ten patients in the second and third presentation categories died, mainly because they were given antibiotics (penicillin derivatives) that did not affect plague. Some of the other patients, although not initially considered to have plague, were given antibiotics with activity against plague.

Some of the other diseases that may be considered in the differential diagnosis of plague include tularemia, meningococcemia (because the ecchymoses and purpura seen can occur with plague meningitis), hemorrhagic smallpox, and diphtheria (because pharyngeal or tonsillar plague can have the appearance of a pseudomembrane, and the appearance of the lymph nodes may be similar to that seen in other bacterial infections). If *Y pestis* is used as a biological weapon, the differential diagnosis of an epidemic of pneumonic plague in its early stages might include tularemia, anthrax infection, or staphylococcal enterotoxin B intoxication.[549]

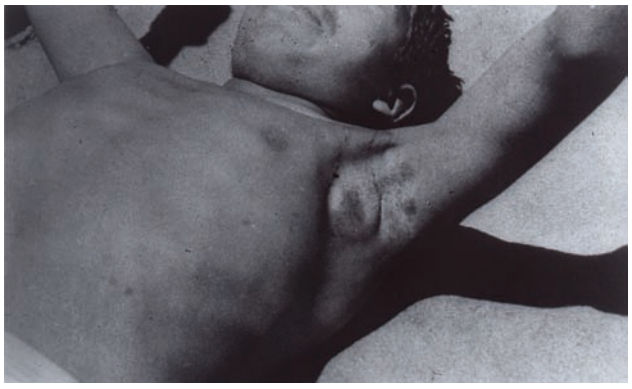

Fig. 35-27. Patient with a bubo. Buboes are extremely tender, and usually involve a lymph node chain draining the site of the infecting flea bite. Although this picture shows a bubo in the armpit, bites are most commonly on the lower extremities, hence femoral nodes are the most common site for buboes.
Photograph: Courtesy of the Armed Forces Institute of Pathology, negative 219900 (7B).

In the field, plague bacilli may be observed in a bubo aspirate or a peripheral blood smear. To aspirate a bubo, one can use a 20 gauge needle with a 10 mL syringe and 1 mL of sterile saline. Saline is first injected with the needle directed toward the periphery of the bubo, then without removing the needle from the skin the syringe is withdrawn a few times until the aspirate becomes blood-tinged. The aspirate can then be used for direct visualization on a slide, using Wayson's or Giemsa stains. The background will appear pink with the Wayson's stain, and the plague bacilli will be appear light blue with dark polar bodies 1 to 2 mm long.[546] They can appear singly or in pairs and can be pleomorphic[538]; they have been described as looking similar to a safety pin.[554]

If more elaborate diagnostic laboratory capabilities exist in the field or in garrison, diagnosis can be confirmed by culture of any involved site on blood and MacConkey agar plates or an infusion broth. Pinpoint colonies may appear on agar after 24 hours at 35°C. The optimal growth rate occurs at 28°C.[546] Serum passive hemagglutination or complement fixation techniques can be used for laboratory confirmation if cultures are unsuccessful.[553] Fluorescent antibody tests on bubo aspirates, sputum, or cerebrospinal fluid can aid in rapid diagnosis if the tests are available.[546]

Recommendations for Therapy and Control

Therapy

According to the World Health Organization expert committee on plague, patients should receive at least 10 days of treatment. Streptomycin is generally considered the drug of choice and is given intramuscularly at a dose of 30 mg/kg daily in two divided doses. Tetracycline 2 to 4 g daily by mouth in four divided doses is an alternative regimen for streptomycin-allergic patients for whom an oral drug is appropriate. Patients who are hypotensive and would have poor intramuscular absorption and those with plague meningitis should receive

chloramphenicol because it can be given intravenously and has superior penetration of the cerebrospinal fluid. A loading dose of 25 mg/kg can be given intravenously, followed by 60 mg/kg per day in four divided doses. As the patient improves, the dose may be given orally and decreased to 30mg/kg per day to lessen bone marrow suppression.[546,560,566]

Because of plague's high case fatality rate, appropriate treatment must be initiated immediately when plague infection is suspected. Efforts to confirm the diagnosis by culture must not delay the initiation of antibiotic therapy. Patients with pneumonic or pharyngeal plague require droplet isolation precautions for at least 48 hours of therapy or until their sputum or throat cultures are negative. Support staff should use masks, gowns, gloves, and eye protection.[62,538] Drainage and secretion precautions should be used for patients with bubonic plague until 48 hours after beginning antimicrobial treatment; sputum, purulent discharges, and soiled articles need to be disinfected. In outbreaks where fleas are involved, patients, their clothing, and their belongings need to be treated with insecticide to kill the fleas.[62]

Control

Although plague is generally restricted to certain geographic areas worldwide, it has the potential to be imported across international boundaries, so public health authorities should maintain an awareness of the worldwide incidence.[543,546] Plague, cholera, and yellow fever are the three internationally quarantinable diseases.[567] Before departing from a country with an ongoing pneumonic plague epidemic, travelers suspected of significant exposure are required by international regulations to be isolated for 6 days. In addition, those arriving in a country on a vessel suspected to be plague-infested may require disinfecting and surveillance for illness for up to 6 days.[62]

Strategies for control, depending on personnel, resources, and extent of spread, include antibiotic treatment of cases, flea control with insecticides, rodent control by poisoning and trapping, proper garbage disposal, proper food storage, rat-proofing of buildings, antibiotic prophylaxis for potential contacts of pneumonic plague, quarantine of human cases, ship inspection in ports, vaccine administration, and education of the population to avoid contacts with rodents, prevent rodent harborage, and control fleas on pets.[62,546] In a bubonic plague outbreak, it is imperative to institute flea-control measures before killing rodents,[62,538] because fleas will leave a dead rodent and search for a new host, increasing the risk of human infection.[552] Pneumonic plague cases must be isolated, and all household and other close contacts should be given antibiotic prophylaxis with tetracycline (15 to 30 mg/kg) or chloramphenicol (30 mg/kg) daily in four divided doses for 1 week after contact. Close contacts of confirmed bubonic plague cases should be appropriately disinfested with insecticide and put under surveillance for signs of infection.[62]

In the absence of an outbreak situation, ongoing surveillance needs to be added to the measures listed above, especially in endemic areas. The US Army Plague Surveillance Program consists of rodent and flea population characterization through trapping rodents and collecting their fleas, rodent population observation, carnivore blood serum collection, and continuous collaboration with local and state health authorities. These measures should provide baseline information for the early recognition of an epizootic and the need for an epizootic investigation.[552]

The licensed, whole cell, formalin-killed vaccine is no longer manufactured in the United States and is therefore no longer available. Individuals in the past who would have been considered for vaccination included laboratory workers, those who frequently handle field or clinical materials that are potentially infected, those who work in the wilderness with limited access to medical care (eg, Army Special Forces personnel, wildlife and fish workers), and those who work or reside in endemic areas, including Peace Corps workers, journalists, photographers, disaster workers,[554] and certain military personnel (eg, Special Forces). The schedule of the licensed vaccine was three intramuscular doses: 1.0 mL initially, then smaller doses of 0.2 mL at 1 to 3 months after the first dose and 5 to 6 months following the second dose. Then 0.2 mL was given at 6 and 12 months following the completion of the initial series and then every 1 to 2 years, if required.

No randomized field trials exist to substantiate the claim that killed plague vaccines are effective in preventing human disease. Indirect evidence of its efficacy have been cited instead: the fact that there were no cases of plague in World War II among vaccinated US troops and only eight cases during the Vietnam War, despite considerable exposure in both instances.[546] About 7% of vaccinees fail to produce adequate antibody following the initial series. Work is being done to find a more effective plague vaccine. Studies using plague subunit vaccines have demonstrated protection of mice against pneumonic disease.[568,569] Despite prior vaccination, someone with a definite exposure should receive prophylac-

tic antibiotics as previously described.[561] In epidemic situations or when risk of contact with infected rodents or fleas is felt to be high, chemoprophylaxis with tetracycline may be indicated.[570] Also, individuals should understand the importance of personal protective measures, including wearing shoes, wearing clothing that covers the legs, using insect repellent, and wearing gloves when handling potentially infected laboratory specimens and when handling ill or dead animals.[556]

With recent concerns about biological terrorism, plague is at the top of both military and civilian threat lists.[571–575] A recent public health consensus panel has published recommendations for public health management of plague if used as a bioterrorist weapon.[576] Plague will continue to be a concern for the US military as long as plague remains a potential biological warfare agent and military operations take place in plague-endemic regions of the world. As the outbreak in India has shown, the Black Death has periodically gone into hiding, only to resurface with a vengeance.[539] Therefore, the US military and public health community must remain vigilant in their surveillance for this disease to avoid unpleasant surprises in the future.

[Mark G. Kortepeter]

FILARIASIS

Introduction and Military Relevance

Five species of roundworms cause significant human filariasis. Of these, three species cause lymphatic filariasis: *Wuchereria bancrofti, Brugia malayi,* and *B timori. Onchocerca volvulus* causes river blindness, and *Loa loa* causes dermal afflictions. Three other species can be found in humans but cause little or no morbidity: *Mansonella streptocerca, M perstans,* and *M ozzardi.*

Because of their incubation periods of several months, the filarial diseases do not have an immediate tactical impact but may have an operational impact. Filarial fevers, adenitis, and retrograde lymphangitis can be debilitating, especially in the case of brugian filariasis. No effective therapy was available during World War II, and high rates were seen among US servicemen in the Pacific theater. In some units, 30% became infected and symptoms included pain and erythema of the scrotum (56%), arms (38%), and legs (14%).[577]

Bancroftian Filariasis

Description of the Pathogen

Adult *W bancrofti* are creamy white worms measuring 80 to 100 mm long (females) or about 40 mm long (males). Bancroftian microfilaria are speciated by identifying a sheath but no caudal nuclei.

Epidemiology

The larvae of *W bancrofti* are transmitted by a mosquito, typically *Culex quinquifaciatus*, *Anopheles gambiae*, *An funestus*, *Aedes polynesienses*, *Ae scapularis*, or *Ae pseudoscutellaris*.[62p197–201] Humans are the sole reservoir of the disease. *W bancrofti* is the most common and widespread of the filarias infecting humans,[577] affecting populations in sub-Saharan Africa, Asia, the Pacific, the Caribbean region, the eastern coastal plains of South America, and portions of Central America.[578] The World Health Organization estimated in 1994 that 751 million people live in areas endemic for lymphatic filariasis. Of those, 72.8 million were infected with *W bancrofti.*[579]

The incidence of filariasis in immunologically naive arrivals to an endemic area can be quite high. In Indonesia, farmers who moved from nonendemic to endemic areas had microfilarial rates of 6% to 35%.[580] As mentioned above, *W bancrofti* infected servicemen in the Pacific theater during World War II. The major difference between these two natural experiments is that the Indonesian farmers stayed in the infected areas and many of them subsequently developed elephantiasis, as opposed to the World War II soldiers who were evacuated from the region with resolution of their symptoms. Thus, it appears that continued reexposure to the organism leads to the more permanent effects of chronic filariasis.

Pathogenesis and Clinical Findings

When an infected mosquito takes a blood meal, the larvae migrate from its mouthparts onto the person's skin. From there the larvae enter the body through the puncture site, and they typically take up residence in the lymphatic vessels. The females produce microfilariae, which reach the bloodstream 6 to 12 months after infection. The pathogenesis is more commonly due to inflammation and blockage of the lymphatic channels by adult worms, which manifest themselves 3 to 12 months after infection, than to the presence of microfilariae.[581]

The spectrum of disease ranges from infection

without symptoms to the chronic effects of blocked lymphatic vessels. Most filarial infections do not cause symptoms,[581] but the asymptomatically infected still serve as a reservoir. The incubation period varies from 6 to 12 months, but allergic reactions can occur 1 month after infection.

Indigenous and nonindigenous peoples display different clinical features. In populations raised in filarial regions, the disease spectrum ranges from asymptomatic with no detectable microfilaremia to such signs of chronic infection as hydrocele, chylurea, or elephantiasis of limbs, genitalia, or breasts. In those with "expatriate syndrome" (when military personnel or other migrants to endemic areas have acquired these infections), the symptoms typically consist of genital pain (from inflammation of the associated lymphatics), lymphangitis, and lymphandenitis, as well as hives, rashes, eosinophilia, and other allergic manifestations.

Tropical pulmonary eosinophilia is an amicrofilaremic lung condition associated with the lymphatic filariases. It is characterized by a primarily nocturnal paroxysmal cough and wheeze with scanty sputum production, occasional weight loss, adenopathy, low-grade fever, and extreme eosinophilia (greater than 3,000/mm^3). If not treated with diethylcarbamazine citrate (DEC), tropical pulmonary eosinophilia can progress to a debilitating, chronic, interstitial lung disease.[582]

Diagnostic Approaches

The gold standard for diagnosing bancroftian filariasis (but not brugian filariasis) is detecting circulating filarial antigen (CFA) in the bloodstream.[583] One CFA assay is a semiqualitative ELISA test that requires technical skill and expensive equipment. A simpler CFA assay is the "card test," which yields positive or negative results. The card test has replaced the more cumbersome method of directly demonstrating the parasite by the examination of nocturnally collected blood samples. A colormetric indicator displays a pink line when the test is positive. The test is inexpensive (less than US $1 per card), useable by nonclinicians, and gives immediate results. Its versatility allows the card test to be a diagnostic tool in both the clinical and field setting.

Recommendations for Therapy and Control

Treatment can be either tailored to an individual patient or designed to eliminate filariasis from a community. For individuals, treatment is with DEC, which kills microfilariae and is toxic to adult worms when given at the doses listed in Exhibit 35-2. If no microfilariae can be found in the blood or skin, then full doses (6 mg/kg per day in 3 doses) can be given beginning on day 1. Variations of treatment include a Brazilian treatment protocol that showed efficacy with DEC at 6 mg/kg per day in single, daily doses for 12 days.[584] Additionally, ivermectin, 20 to 200 mg/kg in a single dose, may be effective in clearing microfilariae but does not affect adult worms.[585]

The side effects of DEC are common and can be profound. An inflammatory response marked by fever, nausea, vomiting, arthralgia, chills, and headache is caused by the DEC-induced disintegration of microfilaria. These side effects are reduced by slowly introducing DEC to patients as described in the above dosing schedule. As with many inflammatory and allergic responses, these side effects can be ameliorated by corticosteroids and antihistamines.[585]

Mass treatment by medicated salt or single annual doses combined with vector control are effective ways to control or even eradicate filariasis in a population. DEC-medicated salt can eliminate lym-

EXHIBIT 35-2

DOSAGES OF DEC FOR TREATING BANCROFTIAN FILARIASIS

	Adult	Child
Day 1	50 mg, taken orally after a meal	1 mg/kg, taken orally after a meal
Day 2	50 mg, three times a day	1 mg/kg, three times a day
Day 3	100 mg, three times a day	1–2 mg/kg, three times a day
Days 4–21	6 mg/kg per day in three doses	6 mg/kg per day in three doses

Source: Drugs for parasitic infection. *Med Lett Drugs Ther.* 1993;35(911):111–122.

phatic filariasis from a population. Regular table salt fortified with 0.3% DEC has been shown to greatly reduce, and even to eliminate in some areas, the incidence of bancroftian filariasis and, to a lesser extent, *B malayi* filariasis.[586] At such a low dose, DEC has no notable side effects.

Another way to treat populations is annual, single-dose treatment. Annual, single doses of ivermectin (400 mg/kg) with DEC (6 mg/kg) have also been shown to reduce prevalence by 32% and microfilarial levels by 96% 12 months after treatment.[587] Annual, single-dose treatment with DEC alone or ivermectin alone has also been shown to be effective.

Vector control will lower the incidence of filariasis. Vectors can be controlled by pesticides, polystyrene beads dropped in latrines, larvicides, and larvae-eating creatures introduced into mosquito-breeding sites. Ultra-low-volume malathion spraying is effective against adult forms of the mosquito.[580] A major vector of *W bancrofti* in urban areas is *C quinquifaciatus*. This domestic mosquito's larvae develop in organically rich waters such as are found in pit latrines. Tossing a 4- to 6-cm layer of polystyrene beads into pit latrines is effective in reducing the incidence of bancroftian filariasis.[588] The polystyrene beads form a floating layer, which carpets the surface of the water. This inhibits the emergence of new mosquitoes, prevents the larvae from breathing, and inhibits ovipositing (Figure 35-28).

Fig. 35-28. Polystyrene beads being deposited into a pit latrine to reduce the incidence of bancroftian filariasis by interfering with the life cycle of the vector mosquitoes. The floating blanket of beads prevents ovipositing and also serves to asphyxiate larvae and prevent emergence of new mosquitoes.
Photograph: Courtesy of Dr. C. F. Curtis.

Larvicides are also useful in controlling the vector. Attacking the vector larvae is an important way to prevent filariasis. In recent years, antilarval products have become more environmental friendly and specifically designed to destroy mosquito larvae. For larvae control, the pest control industry has discontinued the use of organophosphates sprayed on breeding sites. The leading antilarvae substances are either selective bacillary toxins or insect growth regulators.

A popular larvicide is derived from *Bacillus thurengiensis* var. *israelensis* (typically denoted as "Bt" or "Bti"). Pest control personnel disperse Bt products in a variety of ways, to include tossing Bt time-release briquettes into stagnant pools or spraying Bt pellets or a liquid Bt solution by hand or air. A more persistent toxin is derived from *Bacillus sphaericus*. It is well suited for wetland areas and waters with high organic content, such as waste water and dairy lagoons. *B sphaericus* toxin has also been successfully used to kill *C quinquifaciatus* larvae in pit latrines for up to 10 weeks when applied at 10 mg per liter of sewage.[589]

Methoprene is a stable but nonpersistent compound that inhibits the growth of mosquito larvae. Insect growth regulators prevent insects from maturing to the adult stage. This compound is found in slow release briquettes, pellets, and liquids that are effective from 7 to more than 150 days, depending on the specific way the compound is formulated.[590]

Biocontrol is an environmentally friendlier way to control larvae. Introducing larvae-eating creatures, such certain species of ducks and fish, into mosquito-breeding areas can reduce mosquito larvae.

Individuals should use personal protection measures to prevent transmission from the mosquito (see chapter 22, Personal Protection Measures Against Arthropods). The includes wearing permethrin impregnated outerwear, applying 33% DEET insect repellent to exposed skin, and wearing long-sleeved shirts and long pants. Additionally, sleeping under permethrin-impregnated bed nets should help prevent transmission.

Malayan and Timorian Filariasis

Description of the Pathogen

B timori adult females are approximately 30 mm long; males are 17 mm long. The microfilariae have several distinguishing features: they are longer and have a cephalic space with proportions length to width of about 3:1. In addition, the sheath does not

stain pink with Giemsa stain as do those of *B malayi* and *W bancrofti*.

Adult female *B malayi* worms are similar to *W bancrofti* worms except that they are only 43 to 55 mm long. Male worms are 14 to 23 mm long. The microfilariae of *B malayi* are distinguished from those of *W bancrofti* by their two isolated nuclei at the tip of the tail and their absence of nuclei in the cephalic spaces.

Epidemiology

Like bancroftian filariasis, these are also lymphatic filariases transmitted by mosquito bites. *B malayi* is transmitted by species of *Mansonia*, *Anopheles*, and *Aedes*; *B timori* is transmitted by *An barbirostris*. But as is indicated by their names, their geographic range is much more limited. *B timori* is reported from the Lesser Sunda Islands of Indonesia. They both occur in and around Indonesia, although *B malayi* is also found in Malaysia, the Philippines, Sri Lanka, India, Korea, China, Thailand, and Vietnam. *B malayi* is unique in that animals may also serve as reservoirs for some subperiodic strains, but humans are the primary reservoir.[578] The World Health Organization estimated in 1994 that 5.8 million people were infected with *Brugia malayi* or *Brugia timori*.[579]

Diagnostic Approaches and Recommendations for Therapy and Control

Definitive diagnosis occurs by identifying microfilariae in the blood or adult worms in tissue samples. In most cases, the best time to obtain a blood sample is between 2200 and 0200 hours, when microfilaria reach their maximum concentration in the peripheral blood. This nocturnal emergence coincides with the nighttime feeding patterns of the vectors from the *Culex*, *Anopheles*, and *Aedes* species. The microfilariae are virtually undetectable in peripheral blood during the day. A notable exception to this nocturnal periodicity occurs in the South Pacific and foci in Southeast Asia, where microfilariae possess a diurnal periodicity and are more concentrated in the peripheral blood during the day. Not surprisingly, this variant is transmitted by a day-biting mosquito of the *Aedes* species. Concentration techniques assist in isolating microfilariae. After centrifuging 2 mL of blood mixed with 10 mL of 2% formalin, a millipore filter (2 to 5 mm pore size) in a Swinney adapter is used to isolate the microfilariae.[62] Giemsa staining of thick and thin smears allows speciation. A urinalysis may indicate renal abnormalities. More than 50% of microfilaremic patients have microscopic hematuria, proteinuria, or both.[591] The detection of a *B malayi*–specific repetitive DNA sequence by polymerase chain reaction holds promise as an easier way to diagnose malayan filariasis.[592]

Onchocerciasis

Description of the Pathogen

Adult female *Onocerca volvulus* worms are 23 to 70 cm long, whereas the males are 3 to 6 cm long. The microfilariae are unsheathed, possess a sharply pointed tail, and do not have terminal nuclei.

Epidemiology

Onchocerciasis (river blindness) is a chronic, nonfatal disease transmitted by the bite of the female black fly *Simulium damnosum*, which breeds in fast-moving streams and rivers. Humans are the sole reservoir for this disease. Most (95%) of the 17.5 million individuals infected with *O volvulus* live in Africa in a zone between 15° North and 15° South latitude, with one third of global cases living in Nigeria (Figure 35-29). There are small foci in the Western hemisphere, predominantly in Guatemala and Mexico. Smaller foci have been found in Colombia, Venezuela, Brazil, and Ecuador. Cases have also been verified in the southwest tip of the Arabian peninsula in Yemen and Saudi Arabia.[593]

Pathogenesis and Clinical Findings

Like other filarial diseases, onchocerciasis is caused by the direct physical insult of worms in tissues combined with the resultant inflammatory response. The female black fly injects *S damnosum* larvae into the skin, from where they spread to superficial and deep tissues. In those tissues they mature into adult worms, bundled together in characteristic nests. Within 7 to 34 months of the original infection, the females release microfilariae, which commence a grand tour of their human host. The microfilariae migrate to the skin, causing a pruritic rash. Another destination is the ocular tissues, where microfilariae cause blindness in up to 4% of those infected.[594] The disease is characterized by fibrous nodules in subcutaneous tissues, particularly in the head and shoulders (Western hemisphere) or pelvic girdle and lower extremities (Africa).[62] Lichenification and depigmentation can also occur.

Fig. 35-29. This statue, depicting a blind victim of onchocerciasis being led by a young boy, was dedicated at the World Health Organization headquarters in Geneva, Switzerland, on October 6, 1999. The statue commemorates the 25th anniversary of the World Health Organization's Onchocerciasis Control Programme and its success in combating river blindness in western Africa. Photograph: Courtesy of Colonel Patrick W. Kelley, Medical Corps, US Army.

Diagnostic Approaches

Examination of shave biopsies from the hip or scapula will frequently reveal microfilariae. The specimen must soak overnight in normal saline and then be observed unstained under a microscope for microfilarieae. Slit lamp examination of the anterior chamber of the eye may reveal motile microfilariae or corneal lesions. Examining the blood may reveal eosinophilia but rarely microfilariae.

Recommendations for Therapy and Control

Ivermectin, which is well tolerated, will kill the microfilariae but not the adult forms. The dose is 150 mg/kg given once each year for 5 to 10 years. Occasionally, the treated patient will experience a Mazotti-type reaction, which includes fever, tender lymph nodes, headache, pruritis, and joint and bone pain.[581]

Vectors are controlled by applying larvicides to black-fly breeding areas. Spraying temefos (Abate) 0.05 mg/L for 10 minutes in the wet season and 0.10 mg/L for 10 minutes in the dry season can be effective. The toxin derived from *Bacillus therengensis*, Bt H-14, can also be effective at two and a half times the dose for temefos. Bt H-14 needs to be introduced at more points along the river, though, because it has less spreading ability.[62p363–367]

DEET effectively protects humans from black fly bites. The extended formulation of DEET repelled black flies (*Prosimulium mixtum* and *P fuscum*) bites for up to 9 hours on people in a sedentary setting.[595] DEET is also effective against *Simulium damnosum*. By wearing trousers and hooded jackets impregnated with DEET, subjects experienced 90% fewer bites over a 5-day period as compared to subjects wearing only shorts and short-sleeved shirts.[596] In another experiment, a 10% concentration of DEET protected the subjects for 299 minutes against *S damnosum*.[597] Bites can also be avoided by bivouacking away from *Simulium* species breeding sites.

Loaisis

Description of the Pathogen

Adult *Loa loa* worms are semitransparent and threadlike, growing to 50 to 70 mm in length (females) or 30 to 34 mm (males). The microfilariae are sheathed. The caudal nuclei are not isolated but are a continuation of the main body nuclei. The cephalic space is much shorter than that of *B malayi*.

Epidemiology

The *Loa loa* larvae are transmitted to the human host by the bite of the deer fly of the *Chrysops* species. Loiasis occurs in central African rain forests in Nigeria, Cameroon, Chad, the Central African Republic, the Democratic Republic of the Congo (formerly Zaire), Uganda, Angola, and Zambia. Humans are the only reservoir. The prevalence of *Loa loa* microfilaraemia typically ranges from 25% to 33% in endemic areas. Incidence in immunologically naive individuals seems low, indicated by the fact that only 1.9% of children under 5 years of age in one study had microfilaremia.[598]

Pathogenesis and Clinical Findings

The pathology caused by infection with *L loa* is primarily dermal, with less common changes in the heart, kidneys, and brain. The pathogenesis has not

been thoroughly elucidated, but it is probably due to an inflammatory response to the worm.

Like the lymphatic filarial diseases, loiasis has different clinical presentations depending on whether or not the host is native to the area. In natives, infection with adult *L loa* worms causes the characteristic, transient area of erythema and angioedema (Calabar swellings) 5- to 10-cm in diameter, chiefly on the wrists and ankles. Occasionally, a wandering adult worm will move subconjunctivally across the eye. Nonnative visitors manifest prominent signs and symptoms of inflammatory or allergic reactions to the parasites. Frequent Calabar swellings, hives, rashes, and occasionally asthma are the main symptoms.

Diagnostic Approaches

Diagnosis is made by identifying microfilariae in the peripheral blood during the day; the highest density occurs around noon.[598] Nonnative patients often have a greatly elevated eosinophil count (30% to 60% of the total white blood cell count). Elevated filarial antibody titers can also aid in the diagnosis.

Recommendations for Therapy and Control

DEC is the drug of choice and is recommended at the doses listed in Exhibit 35-3. Treatment of heavy infections of *L loa* is sometimes associated with encephalopathy. The risk is reduced by starting with a smaller dose and gradually increasing the dose as indicated above. During treatment, hypersensitivity reactions to the dead and dying parasites are common but can be attenuated with steroids and antihistamines.[62p197–201]

Loiasis can be prevented with a weekly dose of 300 mg of DEC.[62,582] Additionally, personal protection measures and destruction of *Chrysops* breeding areas will reduce the risk of transmission from deer flies.

Streptocerciasis

Streptocerciasis is caused by infection with the filaria *Mansonella streptocerca*. The adult female is 27 mm long and the male is 17 mm long. They are transmitted by the biting midge, *Culicoides grahami*. The disease's distribution is limited to Central and West Africa.

In the same way as other filarial diseases, the organism can induce an intense IgE-mediated allergic reaction. Most of the time, however, there are not symptoms. When present, symptoms are primarily of a dermal nature and include pruritis (the most common), papules, and lichenification.[591]

Streptocerciasis is definitively diagnosed by demonstrating microfilariae in wet mounts prepared from skin snips from the scapula.[599] Adult worms can be identified in tissue sections. Eosinophilia may be present. Microfilariae have not been observed in the blood.

DEC kills both the adult worm and microfilariae. The dose for adults is 2 to 4 mg/kg per day for 21 days.[582] The death of the pathogen causes side effects similar to those seen in other filarial diseases. Most patients experience intense pruritis and papules during treatment.[593]

Others

Mansonella ozzardi causes a typically symptomless filarial infection found only in the New World (eg, southern Mexico, Panama, Brazil, Colombia, Argentina, many Caribbean islands). It is diagnosed by identifying microfilariae in blood or skin snips. DEC is ineffective but a single dose of ivermectin (140 μg/kg) reportedly eliminated microfilariae in a patient.[593]

Mansonella perstans infections are a largely nonpathogenic condition and are found in Africa, the Caribbean region, and Central and South America.

EXHIBIT 35-3

DOSAGES OF DEC FOR TREATING LOIASIS

	Adult	Child
Day 1	50 mg, orally after a meal	1 mg/kg after meal
Day 2	50 mg, three times a day	1 mg/kg three times a day
Day 3	100 mg, three times a day	1-2 mg/kg three times a day
Days 4–21	9 mg/kg per day in three doses	9 mg/kg per day in three doses

Source: Drugs for parasitic infection. *Med Lett Drugs Ther.* 1993;35(911):111–122.

Infection is diagnosed by finding microfilariae in the blood. Unlike other filarial infections, DEC has little effect on *M perstans* infections.[593] The current treatment regimen of 5 to 6 mg/kg per day often must be repeated 8 to 10 times to achieve a cure.[582] However, mebendazole is effective in a dose of 100 mg 2 to 3 times a day for 28 to 45 days.[600]

[William P. Corr]

THE LEISHMANIASES

Introduction and Military Relevance

The leishmaniases are a heterogeneous group of disease syndromes caused by infection with protozoan parasites of the genus *Leishmania*. Worldwide these parasitic infections are responsible for significant morbidity and mortality in civilian populations and are a persistent problem for military forces deployed to endemic areas. Although historically the leishmaniases have never had the major impact on campaigns that malaria has had, they do challenge military physicians with clinical difficulties, including recognition of the different disease syndromes, limitations of diagnostic and treatment options, and activation of latent infection after immunocompromise. The leishmaniases also present challenges for prevention because of the behavior of sand flies; the presence of animal reservoirs; the lack of effective chemoprophylaxis, immunoprophylaxis, or preventive vaccines; and the continual struggle to enforce personal protective measures in military personnel. The risk of leishmaniasis to US service members is directly related to the geographic and seasonal deployment of the force. A potential for hundreds to thousands of cases exists given the right epidemiologic circumstances.

There are three primary clinical syndromes: visceral leishmaniasis (VL), also known as kala-azar; localized cutaneous leishmaniasis (CL), which is usually ulcerative; and mucosal leishmaniasis (ML), also known as espundia. Less commonly seen are other cutaneous syndromes, such as leishmaniasis recidivans (LR), diffuse cutaneous leishmaniasis (DCL), and post–kala-azar dermal leishmaniasis. A variety of nonspecific systemic syndromes—including acute febrile illness, lymphadenopathy (localized, regional, and generalized), and chronic syndromes characterized by malaise, nonspecific gastrointestinal problems, and asthenia—have also been recognized.

It is doubtful if our knowledge of any other tropical parasitic disease owes as much to the activities of military men. A young medical officer in the Indian Army Medical Service, DD Cunningham, wrote the first accurate description of an amastigote from a case of "Delhi Boil" in 1885, although he did not appreciate the protozoan nature of the parasite.[601] A Russian military surgeon, PF Borovsky, provided an accurate description of the parasite in a typical ulcerative lesion (Sart sore) while working in Tashkent in 1898.[602] His work, published in Russian in an obscure military medical journal, went unnoticed until translated into English in 1938.[603] William Boog Leishman, a major in the British Royal Army Medical Corps, was the first to describe amastigotes in the splenic pulp of a young soldier who died after a prolonged febrile illness in London after returning from the station of Dum-Dum near Calcutta, India.[604] Cases of "Dum-Dum fever" had puzzled military physicians for years and were responsible for the morbidity and mortality of hundreds of British soldiers in India. A few months later, Captain Charles Donovan described the same parasites in a splenic smear from a young girl with prolonged fever in Madras, India.[605] Col. H.E. Shortt of the Indian Army Medical Service and his colleagues proved the transmission of *Leishmania donovani* parasites from sand flies to humans in 1942.[606]

World War II

During World War II, approximately 1,000 to 1,500 cases of CL were reported in US forces.[607] Cases were seen in Latin America and North Africa, but the majority of cases occurred in the Persian Gulf Command, mainly in the vicinity of Ahváz, Iran, where an epidemic of 630 cases was reported during one 3-month period in late 1943. Diagnosis and treatment were performed in dispensaries. No military personnel were returned to the United States, failed to perform their usual military duty, or were given a medical discharge because of their infection, but treating these cases still strained medical resources. Over 60% of the local mammalian reservoir hosts, desert gerbils, were found to be infected. Intensive rodent destruction with chloropicrin reduced the incidence of leishmaniasis in the natives in the area from 70% to 0.4%. Cases in American troops declined dramatically as well.

VL occurred in 50 to 75 military personnel, mostly from India, China, and the Mediterranean region.[607] Although not a serious operational problem, individual cases posed significant diagnostic

difficulties for physicians. Inexperience of medical corps officers with the disease led to long delays in diagnosis and inappropriate treatments. Although only one death was due to VL, the morbidity was considerable; most of the men lost over 1 year of active duty time and had prolonged hospitalizations. In a well-studied cohort of 30 individuals, 15 cases originated in India and 15 in the Mediterranean.[608] The shortest incubation period was 3 weeks and the longest was 19 months. The average interval from onset of acute symptoms to definitive diagnosis and specific treatment was 10 weeks (range: 2 to 23 weeks), reflecting the unfamiliarity of physicians with the disease. The abrupt onset of fever and chills was seen in 29 of 30 (96%) cases, leading to an initial diagnosis of malaria. Splenomegaly was found in 27 of 30 (90%) patients on first examination and developed later in the other three. In other servicemen stationed in the Mediterranean region, localized lymphadenopathy was described.[609]

The British experience in East Africa during World War II with VL was more sobering. An outbreak occurred in 30 native troops of the King's African Rifles. The troops were from a nonendemic area of Kenya and were training in an endemic area of northern Kenya in 1941.[610] Fourteen soldiers died—specific treatment was not available—and the rest suffered prolonged illness and hospitalization. Similarly, an outbreak of VL was described in 23 native troops raised in a nonendemic area of the Sudan when they trained and fought in endemic areas of Ethiopia.[611] Initially, medical officers suspected malaria, but later the diagnosis of VL was confirmed. It was thought that the stress of battle activated latent VL in these troops.

Leishmaniasis was not a problem in the Korean War or the Vietnam conflict, as the parasite is not endemic to the Korean peninsula or Southeast Asia.

The Middle East

Both CL and VL were reported in British Marines serving in Aden from 1963 to 1965,[612,613] and systemic syndromes with lymphadenopathy have been described in soldiers from Cyprus and Malta.[614] An epidemic of CL occurred in 95 Israeli soldiers while they trained in the Jordan valley for 30 days during the summer of 1967. The incidence of CL was 50%, with an average of 7.4 lesions per soldier.[615] Another outbreak of CL in 60 (20%) of 296 Israeli soldiers occurred during 6 months in the Negev desert.[616] Well over 100 cases of CL have occurred in soldiers of 211 nationalities of the Multinational Force and Observers in the east Sinai since its operations began in April 1982.[617–620] But the largest recent experience with *Leishmania* and military forces took place during the Iraq-Iran border war (1980-1988). Thousands of cases of zoonotic CL due to *L major* occurred in both armies. CL was such an enormous medical and morale problem in the Iranian Army that 1.2 million soldiers and 240,000 civilians were vaccinated with a live, virulent *L major* parasite in a process called "leishmanization."[621] The Israeli Defense Force also used leishmanization. Unfortunately, leishmanization results in a 5% incidence of active lesions that require drug treatment.

Epidemics of CL have been described in nonimmune soldiers when they are deployed for training or newly based in endemic areas. Deployments to Southwest Asia in 1990 and 1991 during the Persian Gulf War have led to 32 parasitologically confirmed cases of leishmaniasis: 20 cases of CL and 12 cases of atypical "viscerotropic" (VtL) infection. The CL cases were typical in their presentation and response to therapy and were caused by *L major* in those cases where the parasite was characterized. None of the Persian Gulf War patients with VtL had the usual findings of VL but rather had a milder, nonspecific constitutional illness with a wide variety of symptoms.[622,623] The limited number of recognized cases in US service members in Southwest Asia during this time was largely due to the fact that most military personnel were deployed during the winter months (November 1990 to February 1991) when sand fly populations were at their lowest and had returned to the United States by April 1991 before the peak sand fly season (May through September). If the deployment had occurred during the peak months, the number of cases would likely have been much higher.

South America and Panama

In 1978 the British Army established a permanent garrison in Belize of about 1,500 troops who served a 1-year tour of duty. Between 1978 and 1990, there were 306 cases of clinical CL (1.5% of the total personnel deployed), 187 of which were parasitologically confirmed.[624] *L braziliensis* was isolated in 72% and *L mexicana* was isolated in 28% of the 107 samples that were characterized. Most patients presented in Belize during their tour of duty or within 4 months of their return to the United Kingdom. One patient presented 11 months after his return. No cases of ML have been reported.

The Jungle Operations Training Center (JOTC) on the Fort Sherman military reservation in Panama has been the source of the majority of cases of CL

for years.[625–630] The cases are sporadic, with a 1% to 2% attack rate in affected units, although outbreaks with much higher site-specific attack rates are well documented.[631] The JOTC is located within Fort Sherman on the Atlantic side of the Canal Zone, although at least two outbreaks at sites on the Pacific side have been documented as well.

A series of 60 cases of CL in US service members was reported in 1988.[632] They were infected in Panama, Brazil, and Colombia. Among 35 soldiers with a 3-week exposure in Panama at the JOTC, the mean maximum incubation period was 33 days (range: 4 to 81 days). Diagnosis was delayed an average of 93 days after onset of skin lesions because of delay by patients in seeking medical attention (mean: 31 days, range: 0 to 365 days), by medical personnel in considering the diagnosis (mean: 45 days, range: 0 to 425 days), and by laboratories in confirming the diagnosis (mean: 17 days, range: 2 to 120 days). Forty-four patients (73%) developed typical ulcerative lesions of CL, while 16 (27%) developed atypical macular, papular, squamous, or verrucous lesions that were confirmed only by culture.

CL also poses a significant problem in the armed forces of several Central and South American countries. In some cases this has led to significant morale problems as soldiers are unwilling to be deployed to areas where they know exposure risks are high. Outbreaks of CL with attack rates of over 50% highlight the potential of leishmaniasis to affect very large numbers of personnel following a short exposure period.

Ninty-six parasitologically confirmed patients treated at the Walter Reed Army Medical Center, Washington, DC, between 1989 and 1996 have included 83 with CL, 3 with VL, and 10 with VtL.[633] The majority of CL patients acquired their infections in Panama at the JOTC, in French Guinea during jungle training, or in Saudi Arabia during the Persian Gulf War. There have also been three cases of VL in young dependent children infected in Sigonella, Sicily, and one adult case infected near Madrid, Spain. Cases of leishmaniasis in the US military from 1954 to 1998 are presented in Figure 35-30. There have been 735 reported cases, for a mean of 16 cases per year.

Epidemiology

Transmission

The vast majority of leishmaniasis transmission occurs through the bite of infected female sand flies; however, other modes of transmission have been described, including intravenous drug abuse and blood transfusions, as well as congenital, sexual, and laboratory acquired transmission.[634] The primary *Leishmania* species that cause disease in humans and their associated clinical syndromes, animal reservoirs, and geographic distribution are presented in Table 35-11. More detailed information can be found elsewhere.[634–639]

Transmission of the leishmaniases often occurs

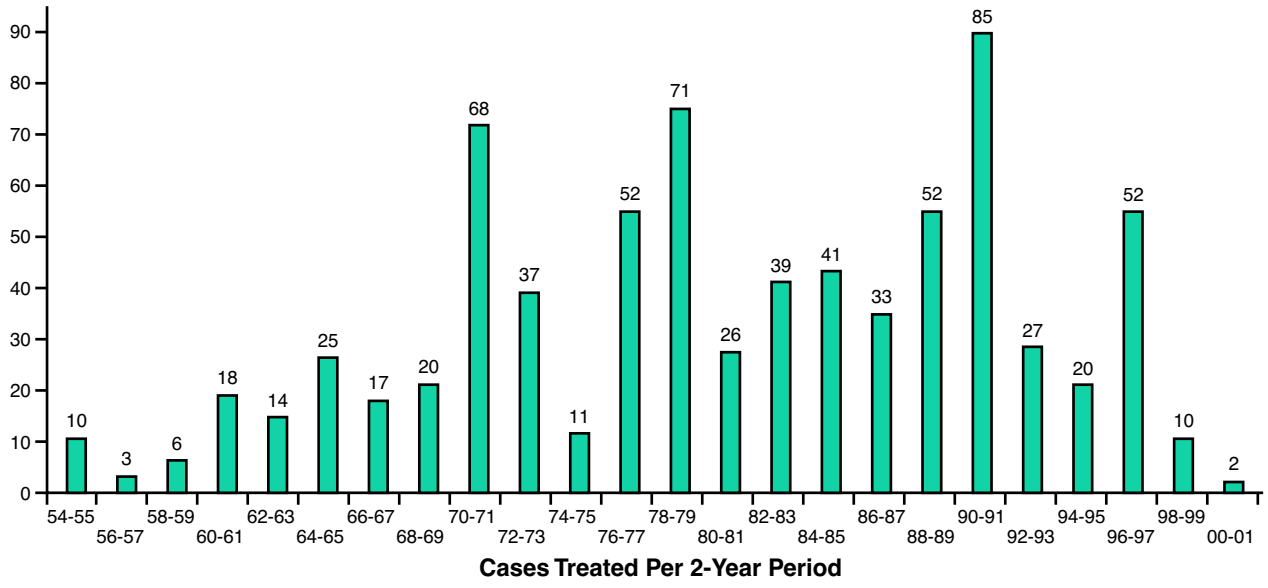

Fig. 35-30. Leishmaniasis in US Military Personnel 1954–1998

TABLE 35-11

PRIMARY LEISHMANIA SPECIES THAT CAUSE DISEASE IN HUMANS, WITH ASSOCIATED ANIMAL RESERVOIRS AND GEOGRAPHIC DISTRIBUTION

Subspecies of *Leishmania*	Primary Clinical Syndrome	Other Clinical Syndromes	Animal Reservoir	Geographic Distribution
Old World				
L donovani	VL	CL, PKDL	Humans?	Epidemic in the Sudan and in the Gangetic plain of India, Nepal, and Bangladesh. Endemic in Iraq, Kenya, and parts of China; sporadic throughout sub-Saharan Africa
L infantum	VL	CL	Dog (and other canines)	Endemic in both the European and African Mediterranean littoral; sporadic in parts of China, SW Asia, and sub-Saharan Africa
L major	CL	ML (uncommon)	Burrowing rodents	Endemic in the Mediterranean littoral of North Africa, the Sahel region of Africa, and most areas of SW and Central Asia
L tropica	CL	VL (India), VtL, LR	Humans?	Focally endemic in North Africa, SW Asia, Central Asia, India, East Africa, Namibia, Turkey, and Greece
L aethiopica	CL	DCL	Hydrax	Ethiopia and Kenya
New World				
L chagasi	VL	CL	Dog	Epidemic in northeast Brazil; focally endemic throughout Central and South America
L mexicana	CL	DCL	Forest rodents	Focally endemic in Texas (USA), Mexico, Dominican Republic, and Central and South America
L amazonensis	CL	ML, DCL, VL	Forest rodents, agouti, opossum	Amazon basin
L braziliensis	CL	ML	Forest rodents?	Focally epidemic and endemic from Mexico to northern Argentina
L guyanensis	CL	ML (uncommon)	Sloth	South America, especially north of the Amazon River
L panamensis	CL	ML (uncommon)	Sloth	Central America, Colombia, Ecuador, Peru, and Venezuela
L peruviana	CL	ML (uncommon)	Rodents, dogs(?)	Peru

CL = cutaneous leishmaniasis, ML = mucosal leishmaniasis ("espundia"), VL = visceral leishmaniasis ("kala-azar"), VtL = viscerotropic leishmaniasis, LR = leishmaniasis recidivans, DCL = diffuse cutaneous leishmaniasis, PKDL = post-kala-azar dermal leishmaniasis

in a very uneven, focal distribution within areas of broad endemicity. This is caused by the behavior and ecology of the anthropophagous species of sand flies (*Phlebotomus* in the Old World and *Lutzomyia* in the New World) and to a lesser extent the density and distribution of the mammalian reservoir animals.[640] Infection risk can vary markedly over just a few hundred meters.

In Panama, sand fly densities are bimodal in distribution, with the highest density at the beginning (May through July) and end (November and December) of the rainy season.[641] Most human infec-

tions tend to occur toward the end of the rainy season. *L panamensis* causes over 90% of the *Leishmania* infections in US soldiers who acquire their infections in Panama. The principal reservoir host is the two-toed sloth, *Choloepus hoffmani*, and at least 4 species of sand flies transmit parasites to humans.

Female sand flies transmit motile, flagellated promastigotes to humans and animals when taking a blood meal. Promastigotes attach to mononuclear phagocytes using specific receptors and are engulfed via endocytosis into endosomes. The endosomes then fuse with lysosomes to form a parasitophorous vacuole. The promastigote transforms into a nonmotile oval structure (2 to 5 mm in diameter) with a degenerate flagella, called the amastigote, inside cells of the mononuclear phagocyte system. *Leishmania* amastigotes are distinguished microscopically from other morphologically similar pathogens by the presence of a rod-shaped kinetoplast in their cytoplasm. Amastigotes persist and replicate by binary fission within the parasitophorous vacuole. Eventually the expanding vacuole fills the cell, leading to lysis and cell death. Released daughter amastigotes attach and penetrate nearby mononuclear cells and disseminate throughout the body. The cycle is continued when feeding sand flies ingest infected cells. The ingested amastigotes transform into promastigotes, which live and develop extracellularly in the alimentary tract of the sand fly (Figure 35-31).

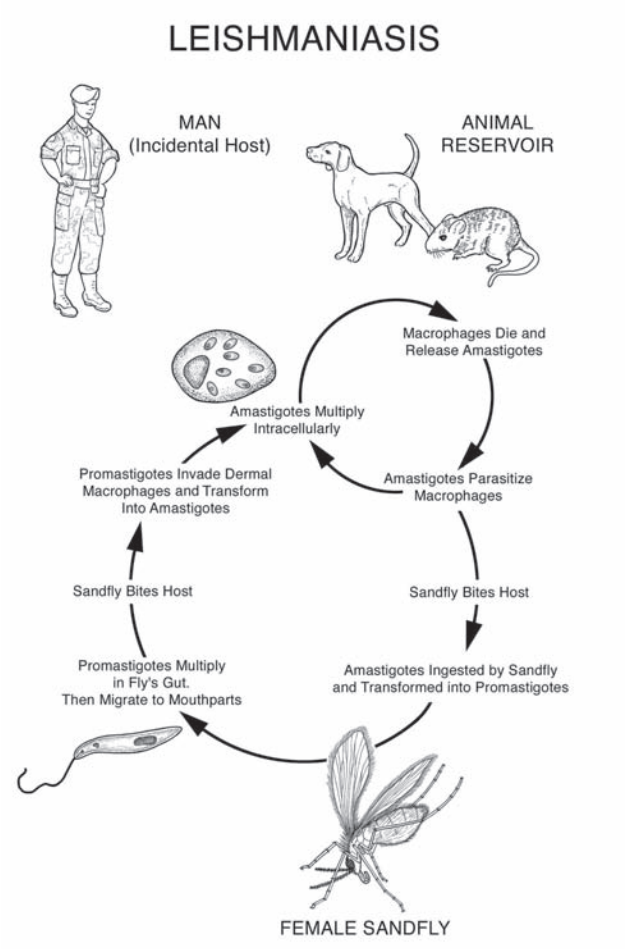

Fig. 35-31. The life cycle of leishmania.
Adapted with permission from: Norton SA, Frankenburg S, Klaus SN. Cutaneous leishmaniasis acquired during military service in the Middle East. *Arch Dermatol*. 1992;128:83

Geographical Distribution

CL of the Old World is often distributed in semiarid, rural, savanna and urban areas, while CL and ML of the New World are seen in humid, neotropical forests. VL is associated with a canine reservoir in the Mediterranean region and in Brazil, but no animal reservoir is associated with VL caused by *L donovani* in the Gangetic plain in southern Asia.

Sand flies are rather delicate and do not survive extremes of temperature and humidity. They exist in harsh climates by seeking cool and humid daytime resting sites such as caves, animal burrows, trees, and dark niches in buildings and rubble. They then emerge at night when ambient temperature drops and humidity increases. Sand flies have short, hopping flight and can travel only a few hundred meters in a night. Seasonal variation in population size can also be quite marked depending largely on rainfall in the tropics and both rainfall and ambient temperatures in more temperate climates.

Incidence

Groups at highest risk of disease following infection are nonimmunes such as military personnel, tourists, settlers, and forest or road workers entering endemic areas. Deforestation, irrigation projects, and migration to cities with peri-urban sprawl are all associated with increased rates and epidemics of leishmaniasis.

Pathogenesis and Clinical Findings

CL is the most common form of leishmaniasis. The incubation period usually ranges from several weeks to months following infection but can be as short as 10 days or as long as 5 years. Ulcers usually resolve spontaneously over several months to years with a disfiguring scar. The typical lesion of ulcerative CL starts as a small, erythematous papule at the bite site.[642] The papule enlarges over sev-

eral weeks, crusts over, and breaks down into a slowly enlarging ulcer. The ulcer can be several centimeters in diameter. It is shallow and well defined and has a raised, erythematous border with central granulation tissue under an exudate. Ulcers may be single or multiple, and surrounding inflammation varies greatly. Ulcers heal with time to give a depressed, hairless, atrophic scar. Involvement of regional draining lymph nodes, the presence of subcutaneous nodules ("sporotrichoid presentations"), and satellite lesions are common. Hyperkeratotic lesions that do not ulcerate can also be seen. A variety of less common presentations have all been reported, including macules; plaques; nodules; and psoriaform, varicelliform, eczematous, and keloidal-like lesions.

ML and LR are chronic, oligoparasitic syndromes associated with persistent and enhanced delayed-type hypersensitivity reactions to leishmanial antigens. ML, most often seen in the New World and associated with *L braziliensis,* is characterized by metastatic involvement of oropharyngeal and nasopharyngeal tissue following a primary ulcerative lesion.[643] Patients may present initially with minor complaints of hoarseness, epistaxis, nasal congestion, and mucopurulent expectoration. The disease progresses slowly over many years and leads to widespread tissue destruction involving the nose, palate, uvula, and hypopharynx. Gross alterations can occur, including septal perforations, irregular vegetative growths, gross swelling, and destruction of the nares, palate, and uvula. Late-stage disease, especially when involving the airway, can be accompanied by persistent cough, hoarseness, or a low muffled voice. Extensive destruction can lead to inspiratory airway compromise and an increase in pulmonary infections because of inability to protect the airway. LR, most often seen in the Old World and associated with *L tropica,* is characterized by recrudescing, brownish-red, lupoid nodules that occur around the periphery of healed primary lesions. These painless lesions may wax and wane for many years.

Diffuse cutaneous leishmaniasis is characterized by disseminated nodules that can be prominent on the head and neck. Lesions appear very similar to those of lepromatous leprosy, but the nodules of lepromatous leprosy are somewhat smaller and are firm to palpation while the nodules of DCL are soft and fleshy to palpation.

Post–kala-azar dermal leishmaniasis is a spectrum of dermatological findings, which includes macules, papules, and nodules following treatment of Indian or African VL with pentavalent antimony. It can occur during, shortly following, or several months after treatment. The initial macules or maculopapular lesions may resolve spontaneously over a few weeks to months or persist and develop into chronic papulonodular lesions. The chronic lesions are rich in parasites, and patients with these lesions are a likely reservoir for anthroponotic (human-sand fly-human) transmission.

Asymptomatic individuals with presumed latent infection can develop localized cutaneous disease at the site of blunt, penetrating, or surgical trauma or disseminated cutaneous lesions if immunosuppressed many years following infection.[644,645]

The classic pentad of clinical findings in VL is fever, wasting, splenomegaly, pancytopenia, and hypergammaglobulinemia. Individuals with culture-proven infection who lack one or more of the classic findings are common in endemic areas. The spectrum of visceralizing infection also includes nonspecific acute and subacute illnesses that can resolve without specific treatment over time.[646–648] These "viscerotropic" infections are poorly documented because of lack of clinical awareness and insensitive parasitologic diagnostic tests. The majority of visceralizing infections have been described as asymptomatic based on skin test surveys of endemic populations. Individuals with a positive reaction to a *Leishmania* skin test antigen without signs or symptoms of disease or a history of classic VL are classified as asymptomatic. It is not possible to determine if these individuals really represent asymptomatic infections or resolved oligosymptomatic disease.

Diagnostic Approaches

The different techniques available to diagnose leishmaniasis are best considered in relation to the concept of parasite burden. Optimal techniques for oligoparasitic syndromes are different from those for polyparasitic syndromes.

Parasitologic diagnosis is defined as any one of these four methods: (1) visualization of amastigotes in Giemsa-stained thin smears, aspirates, impression smears, or histologic sections; (2) isolation of promastigotes in in vitro culture; (3) detection of parasite-specific DNA by hybridization or amplifying parasite-specific DNA with the polymerase chain reaction (PCR); and (4) in vivo culture of parasites (obtaining parasites from tissues of a susceptible animal after inoculation with material from a suspect patient). Giemsa-stained smears are simple and inexpensive but require expert microscopy skills. When amastigotes are unequivocally identified (ie, when the kinetoplast is visualized), the diagnosis is confirmed, but negative Giemsa

smears do not exclude the diagnosis of leishmaniasis. In vitro culture is more sensitive than Giemsa-stained smears and should be viewed as a complementary diagnostic technique. For example, 27% of ulcerative CL lesions in Guatemala were smear negative and culture positive, but in the same study 10% of the cases were positive only by smear.[649] Therefore, in vitro culture and Giemsa-stained smears should both be attempted when possible in all clinically suspect cases. Polymerase chain reaction, although not yet available outside research settings, promises to increase the sensitivity of parasitologic diagnosis.

To obtain an optimal sample from a CL lesion for smear and culture, local anesthesia should be administered with 1% lidocaine plus 1:10,000 epinephrine and a typical ulcerative lesion debrided to remove overlying exudate and crusting. Scrapings, aspirates, and biopsies may be obtained from both the center and border of the ulcer. Scrapings and aspirates are more likely to yield a positive result than biopsy. Increasing the number of cultures from the same lesion also appears to improve sensitivity. In Guatemala, a single culture was positive 38% of the time, but increasing the number to five cultures improved the rate to 66%.[649]

Parasitologic diagnosis of visceralizing syndromes requires an invasive procedure to obtain an appropriate sample from the spleen, bone marrow, or liver and an experienced microscopist to identify amastigotes in tissue or smears. Serologic diagnosis is possible for VL. Antibodies to crude promastigote lysate can be detected by immunofluorescence, agglutination, and enzyme-lined immunosorbent assay. However, antibodies to other pathogens cross-react with the crude lysate used as antigen, and none of the assays are standardized. ELISA-based assays detecting antibodies to K39, a recombinant protein, have proven to be very sensitive and specific for the syndrome of VL.[650–653] Antibodies to K39 can also be detected in a rapid immunochromatographic ("dipstick") format, which yields a result in the field in less than 5 minutes using a drop of whole blood obtained by fingerstick.

Unfortunately, there is no sensitive or specific serologic assay for detecting *Leishmania*-specific antibody for any of the cutaneous leishmaniases. Delayed-type hypersensitivity is present at the time of ulcer formation and persists for years, if not for life, so using hypersensitivity skin tests would help detect prior infection with *Leishmania* and corroborate the diagnosis of oligoparasitic syndromes such as ML and LR. Skin tests are commonly used in endemic countries, but there is no licensed or investigational new drug product available in the United States.

In endemic areas, the specificity of a clinical diagnosis for late-stage VL when the spleen is grossly enlarged is likely quite high. The empiric use of pentavalent antimony in this situation often helps confirm the diagnosis if there is a rapid response (3 to 5 days) characterized by a decline in fever and an improved sense of well-being.

Recommendations for Therapy and Control

Pentavalent antimony has been the mainstay of drug treatment for all the leishmaniases since the 1940s. It is available as sodium stibogluconate (Pentostam, Glaxo Wellcome Foundation, London) and meglumine antimoniate (Glucantime, Aventis Pasteur, Paris). Neither of these drugs is licensed in the United States. Pentostam is available from the Centers for Disease Control and Prevention in Atlanta, Georgia, for civilian use, and from the Walter Reed Army Medical Center in Washington, DC, for all branches of the military. Current recommended treatment regimens for pentavalent antimony are 20 mg/kg per day for 20 days for CL and 20 mg/kg per day for 28 days for VL and ML.[654] The current recommended dose for the treatment of CL acquired in the New World was determined in a randomized trial of Pentostam at 10 mg/kg per day versus 20 mg/kg per day in US soldiers.[655] Pentostam is generally considered a safe and effective drug with no long-term or irreversible toxicity. It is, however, poorly tolerated by most individuals and is associated with headache, myalgias, arthralgias, anorexia, and epigastric pain. Elevated serum amylase and lipase is seen in nearly 100% of treated patients, but clinically significant pancreatitis is uncommon.[656] Optimal drug therapy for immunosuppressed patients is unclear, but they generally require a longer duration of primary therapy or maintenance therapy or both. The practical use of Pentostam[657] and other treatment options are discussed elsewhere.[658,659] No drug treatment eradicates the parasite, so there is always risk of reactivation with future immunosuppression.

The individual service member has the responsibility to prevent the bite of sand flies through the use of personal protection measures, which include frequently applying topical repellents containing 33% DEET, applying permethrin to uniforms, wearing the uniform properly, and sleeping under permethrin-impregnated bednets. Failure to use adequate personal protection measures is contributory to the vast majority of leishmaniasis cases.

When easily identified animal reservoirs are im-

plicated (eg, dogs, burrowing rodents), specific measures to eliminate the reservoir can be successful. Barrier spray applications may prove useful, especially for small military encampments.[406] Personnel should receive predeployment education on the transmission, prevention, and typical clinical presentations of leishmaniasis. Unit commanders and medical personnel should rigorously enforce proper personal protection measures in the field and consider postdeployment surveillance of units with known exposures.

[Alan J. Magill]

TRYPANOSOMIASIS

American Trypanosomiasis (Chagas' Disease)

Introduction

Carlos Chagas discovered the protozoan *Trypanosoma cruzi* in 1909 while studying malaria in Brazil. He found the organism in the intestine of a triatomid and later found the same parasite in the blood of a child suffering from fever, anemia, and lymphadenopathy. Chagas went on to prove that *T cruzi* was indeed the cause of a disease common in certain parts of Brazil. This disease, American trypanosomiasis, or Chagas' disease, is the only disease to be described after its etiologic agent and insect vector were discovered.[660]

Description of the Pathogen

The flagellate protozoan *T cruzi* has a life cycle similar to its *Trypanosomatidae* cousins, *T brucei gambiense* and *T b rhodesiense*, but *T cruzi* has four distinct morphologic forms: an amastigote stage (seen intracellularly in tissue macrophages), a promastigote stage (a transitional stage only), an epimastigote stage (in the midgut of the vector), and a trypomastigote stage (in the feces of the vector). The trypomastigote stage is the infective stage to humans.

The life cycle begins with parasites multiplying (by binary fission) in the midgut of the vector, maturing, and passing as infective forms in the insect's feces. Human infection occurs when insect feces contaminate mucous membranes or breaks in the skin (eg, the puncture wound made by the feeding insect). The parasites then invade host macrophages and other tissue cells, multiply (causing the host cell to rupture), and invade adjacent cells, tissue lymphatics, or the blood stream. The life cycle is complete when an insect vector ingests infected blood.[661]

Epidemiology

Transmission. The insect vector of this disease is a small group of the *Reduviidae* family called the Triatominae or kissing bugs (Figure 35-32). While there are many species of triatomids that will feed on humans, only a few are efficient vectors for Chagas' disease. The four primary vectors in South and Central America are *Panstrongylus megistus*, *Rhodninus prolixus*, *Triatoma infestans*, and *Tri dimidiata*. Local names for these vectors include the *vinchuca* in Argentina and the *bombero* (fireman) in Brazil. Important North American vectors include *Tri barberi* in Mexico and *Tri gerstaeckeri*, *Tri protracta*, and *Tri sanguisuga* in the United States.[662] All species, both male and female, feed at night and often live in the thatched roofs or cracks in the walls or floors of poorly constructed shacks. In fact, children in some parts of Brazil often awaken with spots on their faces that are actually triatomid feces that "rain" down from the thatched roofs during the night.[663]

In addition to vector transmission, Chagas' disease can be transmitted through blood transfusions, organ transplants, transplacental infection, and laboratory accidents.[62p514–520;664] Other routes of transmission have been described in Mexico, where people in some communities believe that the bugs have aphrodisiac powers or that the bug feces can cure warts. In other communities, the triatomid bugs are eaten with hot sauce by the Huichol Indians.[665]

Humans and more than 150 species of wild and

Fig. 35-32. The triatomid vector of American trypanosomiasis, also known as the kissing bug. Photograph: Courtesy of Professor W. Peters, International Institute of Parasitology.

domestic mammals serve as hosts for the parasite. The incubation period is approximately 5 to 14 days after the bite of an infected vector, and the vector becomes infective between 10 and 30 days after biting an infected host. All age groups are susceptible to the parasite, but the young and immunocompromised have the greatest risk for severe disease.[62]

Geographic Distribution. Chagas' disease occurs only in the Western hemisphere, with the vast majority of cases occurring in Latin America. *T cruzi* infection of humans, nonhuman mammals, and reduviid bugs has been found in Mexico and all countries of South and Central America.[661] Although Chagas' disease is found mostly in Latin America, a small number of vector-borne infections acquired in the United States have been reported.[62,661] Additionally, infected triatomids and mammals have been found across the southern part of the United States from Maryland to California.[660] Serological surveys in Washington, DC, demonstrate infection in 4.9% of migrants to that city from Central America.[62]

Incidence. Its prevalence, morbidity, mortality, and incurability make Chagas' disease the most important endemic disease in South America.[666] It is estimated that between 16 million and 18 million people are infected with *T cruzi*[661] and that approximately 50,000 patients die each year from Chagas' disease.[667] Infection can occur at any age but occurs most frequently in infancy. The harmful (often fatal) consequences of infection usually take years to manifest themselves and usually do so in adults. Chagas' disease is the most common cause of myocarditis in South America.[666]

Pathogenesis and Clinical Findings

Three phases of the disease are commonly described: (1) The acute phase can be asymptomatic, can consist of a swelling or "chagoma" at the infection site, or can include fever, malaise, adenopathy, and facial edema (Romana's sign); rarely, acute heart failure or meningoencephalitis can occur. Adults seem more resistant to acute Chagas' disease and usually progress to the next phase of the disease. (2) The indeterminate phase may last for years, in which the infection may be present in tissue without clinical manifestations. (3) The chronic phase may develop into cardiomyopathy, megacolon, or megaesophagus. About 50% of patients with chronic Chagas' disease develop cardiac or gastrointestinal disease. If death occurs during the chronic phase, it is usually due to congestive heart failure, cardiac rupture, or cardiac arrhythmia (eg, ventricular fibrillation, atrioventricular block) secondary to Chagas' cardiomyopathy.[668]

Diagnosis

The diagnosis of acute Chagas' disease is made by detecting parasites in the blood. The parasites can often be seen in wet preparations of buffy coat or anticoagulated blood or in Geimsa-stained smears. If these approaches fail, culturing the parasite in specialized media or by xenodiagnosis (culturing the organism in laboratory-reared insect vectors) may be considered.

The diagnosis of chronic Chagas' disease can be made serologically by detecting IgG specific for *T cruzi* antigen using one or more highly sensitive tests (eg, indirect immunofluorescence, complement fixation, indirect hemagglutination, enzyme-linked immunosorbent assay). A problem with these serologic tests, however, is the false-positive results that occur in patients having diseases such as leishmaniasis, syphilis, malaria, collagen vascular diseases, and other parasitic diseases. Because of this, a definitive diagnosis usually requires a positive result using two or three of the above-mentioned serologic tests.[664]

Recommendations for Therapy and Control

Available drug treatments for *T cruzi* infection are generally unsatisfactory. Two drugs, nifurtimox (available from the Centers for Disease Control and Prevention [CDC], Atlanta, Georgia, on an investigational new drug basis) and benznidazole, are active against both trypomastigotes and amastigotes but are only successful in about 50% of treated patients.[669] Both drugs can cause substantial toxic reactions in treated patients.[670] Though there is no widely accepted treatment for patients with chronic *T cruzi* infection, Gallerano and colleagues have reported that allopurinol is as effective as benznidazole and nifurtimox in suppressing parasitemias.[671] These studies are preliminary, however, and their open and nonrandomized structure makes the interpretation of their findings difficult.

Preventive measures are most important in curbing this disease and include:

- public education on the mode of spread and prevention of the disease,
- effective use of insecticides—especially in poor housing areas where thatched roofs are common,
- use of bednets in infested houses, and

- screening blood and organ donors from endemic areas.[62]

The best way for service members to protect themselves against Chagas' disease is to avoid, if possible, areas and buildings that might harbor the insect vector. If avoidance of these areas is impossible because of mission requirements, service members should practice personal protection measures (eg, the use of deet insect repellent, permethrin-treated uniforms, and permethrin-treated bednets) when operating in high-risk areas.

African Trypanosomiasis (African Sleeping Sickness)

Introduction

Although African trypanosomiasis has probably existed for centuries, it has become a health problem for humans only in the last 150 years. This disease began emerging as a threat to human populations with the colonization of Africa and the spread of the disease from west to east, resulting in its current geographic distribution.[672] An epidemic in Zaire between 1896 and 1906 took approximately 500,000 lives, and another epidemic that occurred along the shores of Lake Victoria around the same time claimed approximately 250,000 lives, two-thirds of the population of the region.[673]

Colonel David Bruce discovered that trypanosomes (*T brucei*) caused a disease in cattle, "nagana," and linked this disease to the tsetse fly in 1895. Forde first saw a trypanosome in the blood of a European in West Africa in 1901; in 1902, Dutton named the parasite *T gambiense*. Castellani then discovered the same parasite in the cerebrospinal fluid of a victim of Ugandan sleeping sickness in 1903. In 1910, Stephens and Fantham discovered a more virulent form of the disease in an English patient in northern Rhodesia who died in just 6 months. They named this form of the disease Rhodesian trypanosomiasis and the parasite *Trypanosoma rhodesiense*. Both parasites were later found to be related to the parasite discovered by Bruce years earlier, *T brucei*.[660,672]

Description of the Pathogen

African trypanosomiasis is caused by the subspecies of the hemoflagellate protozoan, *T brucei*. Gambian, or West African, sleeping sickness is caused by *T brucei gambiense* and is transmitted to humans through the bite of the riverine tsetse fly. Rhodesian, or East African, sleeping sickness is caused by *T b rhodesiense* and is transmitted by the bite of the savannah tsetse fly. These parasites have two distinct morphologic forms: an epimastigote stage (in the salivary glands of the vector) and a trypomastigote stage (in the proboscis of the vector). The trypomastigote stage is the infective stage to humans.[660]

The life cycle of these trypanosomes, like that of *T cruzi* in American trypanosomiasis, begins with the parasite multiplying in the midgut of the vector. These parasites then migrate to the salivary glands of the fly and form epimastigotes, which in turn form metacyclic trypanosomes (young trypomastigotes) that can infect the bite wound of a new host as the vector feeds.[674]

Epidemiology

Transmission. Humans serve as the primary reservoir for *T b gambiense*, while game animals and domestic cattle act as animal reservoirs for *T b rhodesiense*.[62] *T b gambiense* produces a chronic disease after a 2- to 23-day incubation period, while *T b rhodesiense* produces a more severe, acute infection after an incubation period of 1 to 2 weeks.[660]

Of the more than 22 species of tsetse flies in the genus *Glossina*, only six are important in the transmission of trypanosomiasis (Figure 35-33). The important vectors for *T b gambiense* include *G palpalis*, *G fuscipes*, and *G tachinoides*, and the vectors for *T b rhodesiense* include *G morsitans*, *G swynnertoni*, and *G pallidipes*. Both sexes of the tsetse fly feed on blood and are day feeders. They feed on a wide variety of mammals, particularly cattle and other domestic animals, and some reptiles. Humans are incidental

Fig. 35-33. The tsetse fly vector of African trypanosomiasis. Photograph: Courtesy of Colonel Peter Peters, US Army (Retired).

targets for the tsetse fly.[675]

Other modes of disease transmission are possible. Mechanical transmission can occur when a biting fly is interrupted while feeding on an infected host and bites an uninfected host before the blood on the mouth parts has dried (2 to 3 hours).[674] Additionally, congenital transmission has been reported[676] but is rare. Parasite transmission through blood transfusion is also possible but unusual.[674]

Geographic Distribution. African trypanosomiasis is confined to the tropical heart of Africa (between 14° N and 29° S latitude).[677] *T b gambiense* has a much wider-ranging distribution than *T b rhodesiense* and extends from the West Coast of Africa to regions around Lake Victoria. *T b rhodesiense* is confined to the eastern part of the continent and extends from southern Sudan to Mozambique.[660]

Incidence. African sleeping sickness occurs in approximately 200 endemic foci in 36 African countries.[677] There are about 20,000 cases of new human trypanosomiasis reported each year, but experts feel that this is an underestimate due to poor disease surveillance and underreporting.[672,674]

Pathogenesis and Clinical Findings

The pathogenesis of sleeping sickness is thought to be caused by the host's immunological response to the trypanosomes. Initially, there is increased activity in the lymphoid tissue with a proliferation of plasma cells. Large amounts of IgM and autoimmune anti-DNA antibodies are then produced. Next, immune complexes activate physiological cascades resulting in vascular permeability, intravascular coagulopathy, and tissue damage.[672,674]

African trypanosomiasis first manifests as a chancre at the site of the infected tsetse bite 5 to 15 days after the bite. The chancre (which is seldom seen in Africans) appears as a somewhat elevated, painful, and indurated dusky-red papule, approximately 2 to 5 cm in size, which resolves in 2 to 3 weeks.[660,674] Early systemic symptoms include fever, headaches, arthralgias, myalgias, and malaise and are often mistaken for malaria.[672] As the disease progresses, generalized lymphadenopathy follows and often results in enlarged posterior cervical lymph nodes (Winterbottom's sign) in *gambiense* sleeping sickness. Late-stage disease is characterized by central nervous system (CNS) involvement and may occur within weeks to months, depending on the subspecies. CNS manifestations include mood and personality alterations, movement disorders, lassitude, and daytime somnolence. The final stage of the disease consists of pruritis, wasting, and finally coma. Death usually results from the trypanosomiasis itself, infection, or malnutrition. With acute *rhodesiense* disease, the patient may die before CNS involvement of cardiac failure or cardiac arrhythmia due to pancarditis.[674]

Diagnosis

Diagnoses rely on demonstration of trypanosomes in the blood, the chancre, lymph node aspirates, the cerebrospinal fluid, or any combination of these. Concentration techniques, such as centrifugation of the cerebrospinal fluid or buffy-coat microscopy, may increase the sensitivity of the laboratory diagnosis.[672] Another way to increase diagnostic sensitivity is through culture. Blood, cerebrospinal fluid, or lymph node aspirate can be inoculated into a GLSH culture medium.[674] Current serological tests lack the specificity to be used without demonstration of the organism. A commercially available card agglutination test (CATT) has been developed for *T b gambiense* and has been shown to be useful in screening large populations.[672]

While it is impossible to distinguish morphologically between the two subspecies, they can be differentiated. Perhaps the quickest way to distinguish the two subspecies is by taking a good travel history, because there is very little overlap in their geographic distributions. For travelers who have been in areas endemic for both subspecies, animal inoculation can be performed to make the diagnosis. Rodent inoculation of heparinized blood or cerebrospinal fluid is still the most sensitive method for diagnosing infection with *T b rhodesiense*. *T b gambiense* will usually not infect rodents or only infect them with great difficulty.[674]

Recommendations for Therapy and Control

Once the diagnosis is established, treatment should begin immediately. Identification and proper treatment of early disease usually results in cure; untreated sleeping sickness is fatal. If trypanosomes have been demonstrated and there is still doubt about the subspecies, it is recommended that the patients with rapidly progressing disease be treated as having *T b rhodesiense* sleeping sickness and patients with slowly developing symptoms as having *T b gambiense* sleeping sickness.[678]

Suramin, available from the CDC on an investigational basis, is currently the drug of choice for treatment of early sleeping sickness caused by either subspecies. Since this drug does not cross the blood-brain barrier, however, it will not clear trypanosomes from the CNS. Pentamidine is another

drug used in the early treatment of sleeping sickness; it is also used for chemoprophylaxis. Illness caused by *T b rhodesiense* infection, however, often does not respond to pentamidine, so it should be used for the early treatment and prophylaxis of *gambiense* disease only.[678] Melarsoprol (also available from the CDC on an investigational basis) is effective against both subspecies of the parasite and is the drug of choice for treating patients with CNS involvement but is, however, highly toxic and should only be given to patients in a hospital setting. Potential side effects may occur in 5% to 10% of patients and include fever, dermatitis, chest pain, neuropathy, and a fatal toxic encephalopathy.[672,678] If the patient has late-stage disease and *T b gambiense* has been identified as the parasite, eflornithine (available through the World Health Organization, Division of Control of Tropical Diseases) should be used for treatment.[678] Other drugs have been studied for the treatment of African trypanosomiasis (eg, diminazene, nifurtimox, nitrofurazone, melarsonyl potassium), but their toxicity and limited effectiveness curtail their usefulness.[674,678]

Like American trypanosomiasis, African trypanosomiasis is best controlled by preventive measures. They consist of the following:

- education of service members and others on the mode of spread of the disease and how to protect themselves against the tsetse fly,
- use of insecticides and destruction of vector habitats to reduce the fly population,
- disease surveillance in the human host population and prompt treatment for those found to be infected, and
- screening of blood donors from endemic areas.[62]

Chemoprophylaxis with pentamidine (4 mg/kg, to a maximum of 300 mg, intramuscularly every 3 to 6 months) may be indicated for individuals who will have constant, heavy exposure to *T b gambiense*.[672] Service members can best protect themselves from African trypanosomiasis by the same methods used for other vector-borne diseases—vector avoidance and use of personal protective measures (eg, deet, permethrin-treated uniforms, permethrin-treated bednets).

[William C. Hewitson]

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