

**UNIVERSITY OF ORADEA  
FACULTY OF MEDICINE**



**LECTURE NOTES ON TROPICAL MEDICINE**

**Compiled by: Dr. med. Annamaria Antics**

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# MALARIA

## Importance and distribution

Malaria is the most important of all tropical diseases, causing many deaths and much morbidity. It is widely distributed in the tropical and subtropical zones. There are four parasite species that cause human malaria, all of which belong to the genus Plasmodium:

1. *P. falciparum* (malignant tertian malaria, subtertian malaria).
2. *P. vivax* (benign tertian malaria)
3. *P. ovale* (ovale tertian malaria)
4. *P. malariae* (quartan malaria).

## Life cycle.

### Immediately after infection

Malaria is usually transmitted by the bite of an infected female anopheline mosquito.

The infecting agent is the sporozoite, a microscopic spindle-shaped cell which is in mosquito's saliva. Thousands of sporozoites may be injected in a single bite. Infection may also be acquired transplacentally and by blood transfusion or inoculation, via the blood stages of the parasite. The sporozoites disappear from the blood within 8 h, and the successful ones enter polygonal liver cells (hepatocytes). Inside the liver cell the sporozoite divides by asexual fission to form a cyst-like structure called a pre-erythrocytic (PE) schizont, which contains thousands of merozoites. Each merozoite consists of a small mass of nuclear chromatin within a tiny sphere of cytoplasm. The process by which the malaria parasites multiply asexually is called schizogony, whether it takes place in a hepatocyte or in an erythrocyte.

### Tissue schizogony

When the PE schizont is mature, it ruptures and liberates its contained merozoites, these now enter the blood stream and, in the presence of suitable surface receptors, attach themselves to red cells. When they enter the red cells, the process of blood schizogony begins.

It used to be believed that the tendency of patients with *P. vivax* and *P. ovale* malaria to relapse after the blood stages of the parasites had been eliminated was caused by a persistent cycle in the liver. It was thought that some merozoites from the PE schizonts reinvaded liver cells, and that infection could take place from liver cell to liver cell in this way. These second and subsequent generations of liver schizonts were called exoerythrocytic (EE) schizonts. But no one has ever been able to demonstrate them, and the phenomenon of relapse is now explained by the concept of the hypnozoite. So tissue schizogony nowadays is believed to be confined to the initial cycle of multiplication in the liver, in the form of the PE schizont only.

### Prepatent period and relapse: the hypnozoite concept

The time between the bite of the infecting mosquito and the appearance of parasites in the blood is the prepatent period. It is 7-30 days in *P. falciparum* (usually around 10 days), and longer in the other species. It may be very long – in the case of *P. vivax* and *P. ovale* many months or even more than a year. This is believed to be due to the dormant stage of the parasite in the liver. It is as if the sporozoite enters a liver cell and promptly goes to sleep. This dormant stage of the parasite is the hypnozoite. But the dormant parasite has a biological alarm clock, which wakes it from dormancy at a predetermined time. Some strains of parasite “sleep” longer than others.

The hypnozoite concept explains both a prolonged incubation period and the phenomenon of relapse.

### Blood schizogony

Once in the circulation, all species of Plasmodium multiply by asexual multiplication in erythrocytes-blood schizogony (versus tissue schizogony). After entering the red cell, the merozoite begins to feed on the red cell contents, and because it begins to grow, is now called

a trophozoite. Feeding is by ingestion of red-cell stroma and its digestion in a food vacuole. Digested haemoglobin gives rise to a characteristic pigment, malaria pigment (haemozoin), which is present in the cell in increasing amounts as the trophozoite becomes mature. The mature trophozoite begins to divide into separate merozoites within 1-3 days depending on the species, and this process of schizogony is completed in 48 h in the case of *P. falciparum*, *P. vivax* and *P. ovale* and 72 h in the case of *P. malariae*. When fully developed, the schizont ruptures the red cell containing it, and liberates the merozoites into the circulation. These merozoites will then enter new red cells, and this process of asexual replication in the blood tends to proceed, at least in the early stages, in a logarithmic manner. The parasitaemia (the proportion of red cells containing parasites) never increases as rapidly as the number of merozoites in the red cells would suggest, indicating that not all the merozoites succeed in infecting new red cells, or alternatively that not all trophozoites manage to proceed to schizogony and to the release of merozoites.

#### Site and periodicity of schizogony

Schizogony occurs in the circulating blood in the cases of *P. vivax*, *P. ovale* and *P. malariae*, so in all these infections schizonts are commonly seen in the peripheral blood films from infected patients.

In *P. falciparum* schizogony only occurs in capillaries deep within the body. At the stage of the maturing trophozoites, parasite antigens are expressed on the surface of the red cell. Some of these antigens are capable of linking to receptors expressed on the endothelial cells lining capillaries in various organs and tissues of the body. Schizonts of *P. falciparum* are seldom found in peripheral blood films, and when they are it is usually in patients with very severe infections or after splenectomy. Sequestration of enormous numbers of parasites may be responsible for some of the severe manifestations of the disease, such as cerebral malaria, which occur only in *P. falciparum* infections:

The periodicity of schizogony characteristically coincides with paroxysms of fever and this led to the traditional names of the different types of human malaria:

1. Tertian malaria (fever every third day, if the first day is given the number 1): *P. vivax* and *P. ovale*
2. Subtertian malaria (fever slightly more often than every third day): *P. falciparum*
3. Quartan malaria (fever every fourth day if the first day is given the number 1): *P. malariae*.

*P. falciparum* malaria was sometimes called malignant tertian malaria because of its much greater lethal potential than the other tertian malarias. These antique names for malaria are best avoided, not only because they can be confusing, but also because the periodicity they imply often fails to develop. There are many patients who have lost their lives from *P. falciparum* malaria because they never developed the periodic fever, which their doctors wrongly believed to be invariable.

#### Sexual cycle

Some of the merozoites entering red cells do not develop into schizonts, but develop more slowly into solid-looking parasites called gametocytes. These may persist in the circulation for many weeks without destroying the red cells containing them, and they are the forms infective to the mosquito. In each species of malaria, the gametocytes are differentiated into male and female. When the female mosquito swallows the male and female gametocytes in her blood meal, they develop further in her stomach. The male gametocytes rapidly develop to produce spermatozoon-like microgamete, and the female gametocyte becomes the egg like macrogamete.

Fertilization takes place when a microgamete unites with the macrogamete, and this union produces a motile zygote, the ookinete. The ookinete penetrates to the outer surface of the mosquito's stomach and there develops into an oocyst, which comes to contain thousands of sporozoites. When mature, the oocyst ruptures and liberates the sporozoites into the mosquito's body cavity. The sporozoites then migrate forwards to the salivary glands, and are then ready to infect another victim when the mosquito bites. The time elapsing between the ingestion of the gametocytes and the saliva of the mosquito becoming infective by containing sporozoites is called the extrinsic incubation period. It is variable in the different species of parasite, with different mosquito vectors, and with environmental factors, especially temperature. It is never shorter than 10 days and often much longer.

### **Clinical features**

Infections with all the four different malaria species have many clinical features in common. These are related to the liberation of fever-producing substances, especially during schizogony, and the fact that every red cell containing a trophozoite will be destroyed within 48-72 h. the common features are:

- *Fever*: often irregular. Fever is believed to be mediated by host cytokines, which are secreted by leucocytes and other cells in response to a pyrogen or toxin released by rupturing schizonts. The pattern of regularly periodic fever often does not occur until the illness has continued for a week or more. It depends on synchronized schizogony. Why schizogony should ever become synchronized is unknown, but an intriguing explanation has been suggested. High temperatures slow the growth of mature, more than of young, parasites. Fever itself may therefore allow young parasites to 'catch up' with older ones, leading to increasing synchrony with successive cycle.
- *Anaemia*. This is haemolytic in type. It is usually most severe in *P. falciparum* because in this infection cells of all ages can be invaded and even unparasitized red cells may undergo hemolysis. Also, the parasitemia in this infection can be much higher than in others malarial.
- *Splenomegaly*. The spleen enlarges early in the acute attack in all sorts of malaria. When a patient has had many attacks, the spleen may be of enormous size and lead to secondary hypersplenism.
- *Jaundice*. A mild jaundice due to hemolysis may occur in all types of malaria. Severe jaundice only occurs in *P. falciparum* infection, and is due to specific liver involvement.

#### Classical stages of fever

In a paroxysm of malaria, the patient may notice the following stages:

1. A cold stage (the patient shivers or has a frank rigor; the temperature rises sharply)
2. A hot stage (the patient is flushed, has a rapid full pulse, and a high temperature is sustained for a few hours).
3. A sweating stage (the patient sweats freely, or is even drenched, and the temperature falls rapidly).

These stages are most often recognized in *P. vivax* infection. In rare cases, the patient may be afebrile in the presence of a very severe *P. falciparum* infection. Hyperpyrexia may complicate malaria, especially in attacks of *P. falciparum*.

#### Progress of the untreated attack

The natural history of untreated malaria differs with each species.

### **P. falciparum**

Following a single exposure to infection, the patient will either die in the acute attack (a common event) or survive with the development of some immunity and residual anemia. Attacks may recur over the course of the next year (a phenomenon called recrudescence, due to the persistence of blood forms in small numbers between attacks) but then die out spontaneously in the absence of reinfection.

### **P. malariae**

Following a single exposure to infection, and an incubation period that may extend to many weeks, the patient develops a recurrent fever, which occurs at increasing intervals. There may be considerable anemia, and enlargement of the liver and spleen. If no treatment is given to clear the blood forms of the parasite, recrudescence may occur from time to time for more than 30 years. The severity of the attacks tends to diminish as time goes by, until bouts of fever last only a few days.

### **P. vivax and P. ovale**

P. vivax and P. ovale malaria cause very similar illnesses, with bouts of fever which relapse periodically but irregularly over a period of up to 5 years. These are true relapses and not simple recrudescences, because they may occur despite treatment with drugs that entirely eliminate the parasites from the blood. The relapses are due to reinvasion of the blood by merozoites produced when hypnozoites awake from dormancy and develop into PE schizonts.

### Peculiarities of P. falciparum infection

The important difference between P. falciparum and the other plasmodia that infect humans is the capacity of P. falciparum to cause severe (or complicated) disease. Nearly all of the million or more malaria deaths that occur each year result from P. falciparum infections. In endemic areas, most of the clinical impact of P. falciparum infections falls on young children. Nevertheless, the majority of infections cause only a self-limiting febrile illness or, as immunity increases, no illness at all. For reasons that are still not understood, some infections progress to severe disease, and some of these are fatal. In areas with limited or unstable transmission, adults (including tourists) with P. falciparum infection may develop severe or complicated disease, especially if diagnosis is neglected or delayed.

Complicated P. falciparum malaria may take a number of clinical forms. In young children in endemic areas, who suffer the greatest malaria mortality, four clinical syndromes predominate: these are severe anemia, cerebral malaria, acidosis and hypoglycemia. A child may suffer from just one of these complications, or from any combination of them. Other complications seen in adults are unusual in children in endemic areas.

### Cerebral malaria

This is the most important lethal complication of P. falciparum malaria, and occurs only in 'non-immunes'. Its invariable characteristic is a diffuse disturbance of cerebral function, the first manifestations usually being disturbance of consciousness or fits. Focal neurological signs sometimes occur. Untreated, it usually progresses to coma, brain stem failure and death. If recovery does occur, minorities of patients (5-10%) are left with a neurological deficit. Clinically obvious sequelae may resolve over a period of months, but some are permanent. We do not know how many individuals may suffer more subtle impairment (e.g. of memory or intelligence) after cerebral malaria.

Raised intracranial pressure is usual in children with cerebral malaria, but the mechanism for this is not known, and there is no firm evidence that the raised pressure itself

contributes to mortality. Cerebral edema does not appear to be an important feature of cerebral malaria, at least in adults.

A minor degree of disseminated intravascular coagulation (DIC) is common in falciparum malaria, and DIC severe enough to cause bleeding is an occasional complication in adults.

#### Hypoglycemia

Hypoglycemia is a common complication of untreated falciparum malaria in children. It may occur in adults-pregnant women are particularly susceptible. Hypoglycemia may also develop as a complication of quinine or quinidine therapy, probably because these drugs stimulate the pancreas to secrete insulin.

#### Blackwater fever

This obsolete term used to be applied to the syndrome, which sometimes occurs in *P. falciparum* malaria when severe intravascular haemolysis is associated with hemoglobinuria and renal failure. The syndrome still occurs, especially in non-immune adults with severe *P. falciparum* infection. In children in the endemic areas of sub-Saharan Africa, hemoglobinuria sometimes occurs in falciparum malaria, but it is rarely accompanied by renal failure.

#### Malaria in pregnancy

All types of malarial infection can lead to abortion. In *P. falciparum* infection, even in women normally immune, pregnancy is associated with an increased likelihood of developing parasitemia and with higher parasite densities, especially in the first pregnancy. Anemia is a common consequence, and many women enter labour with dangerously low hemoglobin. Organ complication such as coma and renal failure are rare in pregnant women living in endemic areas, but among the non-immune, pregnant women are liable to the same complications as other adults.

*P. falciparum* in endemic areas is an important cause of low birth weight, especially in first-pregnancy babies, who are then at increased risk of dying in infancy from any of a variety of causes. Low birth weight due to maternal malaria presumably results from the fact that the placenta becomes packed with late-stage parasites, especially in the first pregnancy.

In endemic areas it is common to find malaria parasites in umbilical venous blood; it is less common to find them in the neonate's peripheral blood, and these usually disappear within the first 2 days of life. Illness due to congenital infection is rare in endemic areas, but may develop in infants born to non-immune mothers. *P. vivax* is a more common cause of congenital malaria than *P. falciparum*: the illness presents within a few days or weeks of birth with fever, hemolytic anemia and failure to thrive.

#### Immunity in malaria

Immunity in malaria is most pronounced in *P. falciparum* infection. In areas of very high transmission, if a child survives to the age of 5 or 6 years, he or she is likely to have achieved a high degree of immunity to the lethal effects of the infection. This immunity has two main components: an ability to limit parasitemia by the development of specific protective immunoglobulin (IgG) and cell-mediated immunity (antiparasitic immunity), and a physiological tolerance such that low parasitemia produces no fever or subjective illness (antitoxic immunity). In order to maintain this immunity, frequent re-exposure to infection is required. If re-exposure does not occur, the immunity wanes over a period of a few years. Although West African students living in the UK gradually lose their protective antibodies over a 5-year period, they rapidly regain immunity on re-exposure to infection, but the price

may well be two or more severe attacks of malaria on first returning home. The development of a high degree of immunity in an entire population exposed to high levels of *P. falciparum* infection has an extremely important effect on the epidemiology of the infection.

Naturally acquired immunity may be suppressed not only by pregnancy but also by surgery, severe illness of any type and immunosuppressive drugs. However, most studies so far have failed to show increased susceptibility to malaria infection or disease in persons with human immunodeficiency virus (HIV) infection or even in those with acquired immunodeficiency syndrome (AIDS).

#### Non-immune protective factors in malaria

There are several non-immune factors, which affect susceptibility to malaria. *P. vivax* is unable to infect red cells lacking the Duffy blood-group antigen. This is believed to account for the natural resistance of those of pure Negro race to infection with this parasite.

Evidence that G6PD deficiency has a similar protective effect does exist, but is less striking.

Sickle-cell anemia itself is not protective, for malarial infection is disastrous in such patients.

There is now good evidence that the B-thalassemia trait confers protection against *P. falciparum*. There is also strong circumstantial evidence that malnutrition protects against the lethal effects of *P. falciparum* infection.

### **Diagnosis**

#### Direct diagnosis

The specific diagnosis of malaria is made by examining the blood, by making a film, drying and staining it. A Romanowsky stain is used, so that the cytoplasm of the parasites stains blue and their nuclear chromatin red. The optimum pH for staining is 7.2, which usually requires the use of buffered water as a diluent. The main stains used are:

1. Field's stain: a rapid method used for staining single thick films only.
2. Leishman's stain: a fixing/staining method suitable for staining single thin films.
3. Giemsa's stain: for staining thin films (after fixation with methanol) and thick films. It is particularly suitable when many films have to be stained together, such as in survey work.

#### Thick versus thin films

The thin blood film shows the undistorted parasites within the red cells. It is most useful in the detailed study of parasite morphology and species identification. Its disadvantage is that it requires a very prolonged search to detect a low parasitemia, so its sensitivity is low. A patient may have a fever due to *P. falciparum* and yet have no parasites detected by searching the film for half an hour.

The thick film, in which cells are piled upon each other 10-20 deep and lysed and stained at the same time, allows far more red cells to be examined at a time, but it has the disadvantage that the parasites in the lysed cells are distorted. Although readily recognizable as malaria parasites, their specific features of identification may be ambiguous or entirely lost. Only in difficult cases will uncertainty have to be resolved by examining the thin film as well.

#### Serodiagnosis

Serodiagnosis of malaria is of no use for diagnosis of the acute attack. It depends on finding specific antibodies, and most methods in common use are incapable of distinguishing between antibodies to the different species of parasite. Antibodies may be detectable for several years after the last attack of malaria. The main use of serodiagnosis is in excluding

malaria in a patient suffering from recurrent bouts of fever who does not present during a bout. This problem is most commonly met in old soldiers. Serology may also be used in survey as an approximate measure of exposure of a population to malaria. The most frequently used serological technique is the indirect fluorescent antibody test (IFAT).

#### New methods of diagnosis

Many new techniques for identifying malaria parasites are being developed. The quantitative buffy coat (QBC) technique makes use of the fact that parasitized erythrocytes have a different specific gravity from unparasitized red cells and can therefore be looked for in a particular segment of the blood in a centrifuged capillary tube. A dipstick method is now being marketed, by which parasite antigens are detected by placing a drop of blood on a dipstick impregnated with antibody. Polymerase chain reaction (PCR) can be used to detect parasite DNA. At present these are research tools, but their incorporation into clinical practice is probably imminent.

### **Treatment: general**

The treatment of a patient with malaria is supportive and specific.

#### Supportive treatment

Supportive treatment may include:

1. Reducing the temperature if hyperpyrexia is present-especially common with *P. falciparum* infection.
2. Rehydration, especially when vomiting and diarrhoea have been prominent. Overhydration must be carefully avoided, by weighing the patient if possible.
3. Monitoring renal output and taking corrective measures if necessary.
4. Monitoring the hemoglobin: blood transfusion, which is sometimes life-saving should only be given when there are strong clinical indications. In most patients the hemoglobin rises rapidly when the attack has been terminated by specific chemotherapy.
5. Terminating convulsions with appropriate drugs.
6. Monitoring of blood glucose and correction of hypoglycemia where necessary.
7. Treating DIC if this complication is severe enough to cause bleeding; fresh whole blood, platelet-rich plasma and fresh frozen plasma may be given according to availability.
8. Reducing acidemia: usually rehydration and antimalarial therapy are sufficient for this purpose. The use of bicarbonate infusion is not of proven benefit, but may be attempted with care in severe acidosis.

#### Specific chemotherapy

Specific treatment is directed to terminating the parasitemia as rapidly as possible. The drug of choice depends on national policy in the country where you work, and on the likely place of origin of the patient's parasites. Drug resistance is an increasing problem throughout the world, and the picture changes with time; in some countries multidrug resistance threatens to make malaria untreatable, and new additions to the armamentarium of drugs are urgently needed.

Drugs that prevent the development of the blood stages that are causing the illness are traditionally called schizonticides. Some of them also act against the gametocytes of some species, but this has no relevance to the clinical situation. Some of the schizonticides have useful anti-inflammatory effects also.

The most widely used schizonticides has until recently been chloroquine, but the spread of parasite chloroquine resistance has limited the use of this drug in recent years. However, chloroquine remains the first-line treatment for non-severe falciparum malaria in some semi-immune populations in Africa, and it is the drug of choice for all non-falciparum malarias, although early reports of *P. vivax* resistance to chloroquine are appearing.

Effective drugs:

- Chloroquine
- Amodiaquine
- Quinine
- Fansidar (sulfadoxine-pyrimethamine) – for treatment of chloroquine resistant *P. falciparum* infections
- Mefloquine (effective against most multidrug-resistant strains of *P. falciparum*)
- Halofantrine (also active against multidrug-resistant *P. falciparum*)
- Primaquine (for radical cure of relapsing forms of malaria)

#### Chemoprophylaxis

Chemoprophylaxis of malaria involves the regular administration of drugs to prevent clinical symptoms. Drugs taken this way act in two ways: as schizonticides, so that when the parasites enter the red cells they are destroyed, and causal prophylactics. Causal prophylactics prevent the development of the PE schizonts in the liver, and they may also have blood schizonticidal effects. The practical importance of these two modes of action has only become apparent fairly recently, when it was discovered that some drugs might have a much greater effectiveness when given as causal prophylactics, i.e. before sporozoite challenge rather than afterwards.

One must always remember that chemoprophylaxis never provides complete protection against malaria. Everyone embarking on it should be aware of this.

**Proguanil** – is the safest of all antimalarials. It is used a prophylactic only.

**Pyrimethamine (Daraprim, Malocide)** – it is used by itself for suppression only.

#### **Mefloquine prophylaxis**

- As a result of the spread of chloroquine resistance around the world, mefloquine (alone) is now the prophylactic drug of choice for many areas. Initial anxieties about drug accumulation have diminished, and it is now acceptable to recommend an adult dose of 250 mg weekly for periods of a year or more.

#### **Doxycycline**

- This long-acting tetracycline is an effective prophylactic against malaria in a dose of 100 mg daily. It is useful in areas where there is resistance to both chloroquine and mefloquine. It should not be used in pregnancy or lactation, or in young children. An occasional toxic effect is a rash due to photosensitization.

#### **Pyrimethamine-dapsone (Maloprim)**

- This combination drug has occasionally caused agranulocytosis. Its use in prophylaxis is therefore limited to areas where *P. falciparum* is resistant to both chloroquine and mefloquine, and where the risk of contracting *P. falciparum* infection is high. The dose of Maloprim should not exceed one tablet per week.

Fansidar is not used for prophylaxis because of the risk of Stevens-Johnson syndrome. Amodiaquine should be avoided because of a risk of marrow aplasia.

## **Epidemiology**

The epidemiology of malaria has been most studied in the case of *P. falciparum*. The two most important factors are:

1. Intensity of transmission (the number of infective bites per year)
2. The immune response of the host

### Measuring malaria in a community

#### Traditional methods

It has been customary in the past to characterize the epidemiological situation in a community by describing its malarionometric indices. These are established by surveys which, by examining all age groups of the population, determine for each group:

1. The parasite rate (the proportion of blood films which are positive)
2. The spleen rate (the proportion of the group with enlargement of the spleen).

Obviously, both these indices may show seasonal variations. In the case of the spleen rate, its reliability will depend on whether or not there are other diseases in the population, which can cause enlargement of the spleen, such as schistosomiasis and visceral leishmaniasis. The measurement of spleen size is of much less importance.

### Morbidity and mortality

It is now recognized that parasite and spleen rates are measures of malaria infection, reflecting the intensity of transmission, but they are not measures of the clinical impact of malaria on the community. It is the morbidity and mortality attributable to malaria that are important as the basis for designing a malaria control program, and these indicators are equally important in monitoring the effectiveness of control.

Regarding mortality, only an approximate measure can be obtained.

Malarial morbidity can be assessed by prospective studies of cohorts of people for episodes of fever, by health centre and hospital records of severe disease, and by cross-sectional surveys of a population measuring hemoglobin levels to identify malarial anemia. The proportion of first babies that are of low birth weight is an indirect measure of the prevalence of malaria in the primigravid women of a community.

### Stable malaria

Transmission occurs for at least 6 months in the year and is intense. Malarial infection is acquired repeatedly. Children suffer repeated attacks of malaria from the age of a few months onwards (very young children are partly protected by passive immunity acquired by transplacental passage of protective maternal IgG). This may modify the severity of the first few attacks, so allowing them to develop some active immunity while still partly protected. Children reaching the age of 5 or 6 years have substantial immunity, but the price of this immunity is that some children will die of malaria before immunity develops. The proportion who do so is likely to depend on many factors, including the intensity of transmission, the availability of drugs and the prevalence of parasite drug resistance. Data on the actual death toll in different populations are still rarely available.

In areas of stable malaria, the adult population is little affected. As a result the effects on the working population and the economy are slight.

There is little variation in the incidence of malaria from year to year but there may still be pronounced seasonal fluctuations in new cases seen in children. In such an area, there is

often a marked rise in the number of children seen with cerebral malaria about 2 weeks after the rains begin.

#### *Traditional malarionometric indices in stable malaria*

The spleen rate is typically high in young children, reflecting the high frequency of infections in this age group. A spleen rate of 75% in children aged 2-6 years is usual, and the rate may be even higher. With the development of immunity the rate falls progressively with increasing age, and the spleen rate in adults is low.

The parasite rate is high at all ages: the rate in children is often 90% or more. In adults the rate remains high (commonly 50% or more) but the density of parasitemia is low in most adults. This is a reflection of the combination of antiparasitic and antitoxic immunity.

#### Global malaria eradication

For many years global malaria eradication was the aim of the World Health Organization (WHO) and was believed to be feasible because of the invention of dichlorodiphenyltrichloroethane (DDT). Based on periodic house-spraying with DDT, and the idea that if the life span of the female anopheline vector could be reduced below 10 days (the minimum extrinsic incubation period), then even if a mosquito had fed on a gametocyte carrier, she would not have time to become infective before her death. Eradication relied on the following assumptions:

1. It would be possible periodically to spray all dwellings in endemic areas.
2. The mosquitoes would rest on sprayed surface after taking a blood meal (and so be exposed to the insecticide).
3. The mosquitoes would remain sensitive to the lethal effects of DDT.
4. Individuals would cooperate.
5. Nations would collaborate in both spraying and submitting to treatment with gametocytocidal drugs.

#### Failure of global eradication

Eradication has only succeeded in a few areas, mostly islands. The main causes of failure have been:

1. *Operational*: not all houses were sprayed. There are many causes for this, including lack of cooperation, poor mapping, accelerated destruction of thatched roofs (DDT kills caterpillars and their predators; caterpillars soon reappear soon reappear but predators do not) and resentment of intrusion into privacy.
2. *Technical*: resistance of mosquito to insecticide
3. *Political*: failure of countries of cooperate; civil war and severe political unrest; political and administrative incompetence.
4. Failure to convince the people of the need for the programme.

## **TYPHOID AND PARATYPHOID FEVERS (ENTERIC FEVERS)**

The terms typhoid and paratyphoid fevers define those illnesses caused by *Salmonella typhi* and *S. paratyphi* A, B, and C. They all often cause a systemic, septicaemic illness, but so sometimes do the many zoonotic salmonellas which more usually cause *Salmonella* food poisoning.

Typhoid and paratyphoid organisms are cosmopolitan in distribution, but are commonest where standards of personal and environmental hygiene are low. Only to this extent are these diseases tropical.

### Organisms

The causal organisms are all Gram-negative bacilli with flagella. All possess somatic (O) and flagellar (H) antigens. *S. typhi* and *S. paratyphi* C sometimes possess a surface (Vi) antigen that coats the O antigen and potentially protects it from antibody attack.

*S. typhi* and *S. paratyphi* A and B usually infect only humans. *S. paratyphi* C may affect a variety of animals also.

### Mode of infection

This is virtually always by ingestion. Infection may be transmitted in water (mainly *S. typhi*) and food, and is largely dose-related. Ingestion of a fairly small dose of *S. typhi*, such as  $10^5$  organisms, may cause a relatively low attack rate with a fairly long incubation period. But increasing the infecting dose to  $10^9$  organisms raises the attack rate to 95% and greatly shortens the incubation period. High gastric acidity opposes infection.

All these organisms can multiply in suitable foods maintained at a favourable temperature, and so greatly enhance the efficiency of human food-handlers in transmitting the infection. The most important reservoirs of infection are asymptomatic human carriers.

### Typhoid fever

After ingestion, the organisms attach to the small intestinal mucosa, penetrate it and are transported by the lymphatics to mesenteric lymph glands. There they multiply, and enter the blood stream via the thoracic duct. The main location of bacilli is inside macrophages. From this bacteraemia, which corresponds to the end of the incubation period, organisms are carried to the bone marrow, spleen, liver and gallbladder.

There is now a secondary invasion of the bowel via the infected bile. Organisms multiply in macrophages, and pathological changes are greatest where macrophages are present in large numbers, such as in the intestinal lymph follicles. The largest of these are Peyer's patches in the ileum.

There is now a strong inflammatory response with infiltration by inflammatory cells and the Peyer's patches become hyperplastic. If inflammation does not resolve, necrosis occurs within 7-10 days and the patches ulcerate. Involvement of blood vessels may lead to bleeding and, if the whole thickness of the bowel is involved, perforation follows.

Elsewhere in the body, foci of inflammation with macrophages and lymphocytes, so-called typhoid nodules, are scattered in various organs, especially the liver, spleen, marrow and lymph glands.

The natural course of the disease is very variable. In a classical case, fever has returned to normal at the end of the third week and repair processes then begin. In some cases fever may continue for many weeks, and others are abortive, with a brief and unspectacular course.

Death most commonly results from perforation, haemorrhage or toxæmia, occasionally from other complications such as meningitis.

No doubt much of the pathology is due to the obvious local inflammatory response to the bacilli, as in the gut. But serious disease of brain, lung and kidneys is not usually accompanied by typhoid nodule formation, and the assumption is that some unidentified toxin must be the cause. The well-studied *S. typhi* endotoxin does not seem to be the culprit.

### **Clinical picture**

The incubation period is about 14 days on average, but can vary from less than a week to more than 3 weeks. The only almost constant symptoms are fever and headache. The untreated illness normally runs its course in about 3 weeks but can extend to months in exceptional cases.

#### *Classical pattern of fever*

The onset is usually gradual, and rigors are unusual. Fever increases day by day in the first week, often with an evening rise. A remittent fever then continues for another week or more, then falls by lysis in the third week.

The pulse rate usually is relatively slow compared with the fever, and may not reach 100 beats/min even when the temperature is 40°C.

#### *Others symptoms in uncomplicated cases*

Patients with typhoid usually feel very unwell in general, with malaise, generalised aches and pains, and anorexia, the following symptoms are also common:

1. Abdominal pain or discomfort
2. Constipation
3. Diarrhoea
4. Deafness
5. Cough

#### *Physical signs*

These depend not only on the severity of the illness but on the length of time the patient has been ill.

In patients who seek medical aid early, there has usually been no significant dehydration from diarrhoea, and the patient often looks relatively well and is mentally alert. In contrast, the patient who presents after 2 weeks of illness is often very toxic, mentally stuporose and gravely dehydrated. The commonest signs are: fever, a disproportionately slow pulse, hepatomegaly, often tender; mental changes; signs of bronchitis; rose spots; deafness; meningism.

Rose spots can only be seen in fair-skinned patients. They are found from day 7 onwards and take the form of pink macules, usually scanty, mainly on the trunk. They fade on pressure from a glass slide.

Enlargement of the liver and spleen occurs after only a few days of illness, but may be delayed.

### ***Complications***

These may develop as the illness progresses, and they may follow a clinically mild attack. So the clinician must remember that typhoid patients may present with the complication itself, rather than with the symptoms of typhoid fever. These patients are often difficult diagnostic problems.

1. *Perforation*. This typically occurs in the third week. Toxic patients show few signs of peritonitis, except for abdominal distension, increasing toxæmia and rising pulse. Surgery is nowadays considered to give a better chance of survival than conservative management, and excision or segmental resection is safer than simple suturing, for the gut wall immediately surrounding the perforation may be too friable to hold sutures.
2. *Haemorrhage*. This is also typically a complication of the third week. There may be massive bleeding or repeated small bleeds. Surgery is seldom needed provided blood transfusion is available.
3. *Haemolytic anaemia*. This is common in patients with G6PD deficiency and typhoid depresses G6PD levels in normal as well as in deficient patients.
4. *Typhoid lobar pneumonia*. This is a rare complication of the second and third week. Rusty sputum is not produced.
5. *Meningitis*. This may be the only obvious manifestation of typhoid, when it resembles any other pyogenic meningitis.
6. *Renal disease*. This may present as renal failure or an acute nephrotic syndrome, and is probably an immune-complex nephritis. Recovery after successful chemotherapy is usual.
7. *Typhoid abscess*. This is a late complication that can occur almost anywhere, especially in the spleen, liver, brain, breast and skeletal system.
8. *Skeletal complications*. These are mainly suppurative arthritis and osteomyelitis. Both may be greatly delayed in onset. Zenker's degeneration of muscle or polymyositis may occur.
9. *Other complications or sequelae*. These include suppurative parotitis, acute cholecystitis, deep venous thrombosis and the Guillain-Barre syndrome.

### **Diagnosis**

#### Culture

Culture of the organism is the mainstay of diagnosis. Unfortunately, this technology is often lacking in those hospitals in developing countries that most need it.

Blood culture is usually regarded as the most useful technique in the first week, but may be positive at any later stage. A significantly higher rate of positivity occurs with marrow culture even if chemotherapy has been started.

Stool culture often becomes positive in the second week, or earlier if the patient has diarrhoea. Recently a string capsule used to sample duodenal contents has been found to give a much better culture-positive rate (86 versus 42%) than blood culture.

Urine culture becomes positive in about 25% of cases after the second week, but its main use is in the detection of urinary carriers.

Other materials, such as aspirates from rose spots, CSF or pus from abscesses, also yield positive culture results at time.

#### Serodiagnosis

The most widely used test is the Widal test, which measures agglutinating antibodies to the somatic (O) and flagellar (H) antigens.

The test is essentially non-specific, because numerous non-typhoid salmonella share O and H antigens with *S. typhi*. Its usefulness is greatly diminished by three other factors:

1. H antibody titres remain high for a long time after typhoid immunization.

2. In typhoid patients titres often rise before the clinical onset, making it very difficult to demonstrate the diagnostic fourfold rise between initial and subsequent specimens.
3. A significant number of culture-positive patients develop no rise in titre at all.

But if the test is interpreted intelligently, bearing all these facts in mind, a significant number of patients will be correctly diagnosed by the Widal test, when all other methods have failed.

Tests for detecting *S. typhi* antigen in serum, potentially far more useful, are still in their infancy.

#### Other laboratory findings

The WBC is usually within the normal range, as is the differential count, but there may be leucopenia or leucocytosis, and relative lymphocytosis is common.

Biochemical tests usually show only minor changes, such as slight elevation of transaminases and bilirubin. A considerable elevation of indirect bilirubin is often associated with haemolytic anemia in patients with G6PD deficiency and in children.

#### Treatment

Good nursing care is essential, for patients are often desperately ill and mentally uncooperative on first admission, and needed attention to all their bodily needs. A high quality of good supportive medical care – as in the maintenance of fluid and electrolyte balance – is also vital to achieve good survival rates. But the mainstay of treatment is effective antimicrobial chemotherapy.

#### Chemotherapy

Chloramphenicol used to be acknowledged everywhere as the drug of choice. But in recent years resistance has been reported and in some places resistance is now a major problem: in Bangkok almost half of all strains are chloramphenicol-resistant and significant numbers of cases are also resistant to ampicillin and cotrimoxazole. Resistance to all three drugs may occur in 40% of all cases in parts of the Indian subcontinent.

The newer quinolone antibiotics such as ciprofloxacin, ofloxacin and norfloxacin are usually effective, but even with them, resistance has been reported. A 5-7 day course of a third-generation cephalosporin such as ceftriaxone is effective in multidrug-resistant strains, but the relapse rate is uncertain.

Chloramphenicol is bacteriostatic only. A fairly prolonged course must be given to prevent relapse, such as a total of 14 days, or 12 days after fever has abated. This remains the drug of choice in Africa and Papua New Guinea.

Amoxicillin is more expensive than chloramphenicol, but at least as effective if given in high doses, and essential where there is chloramphenicol resistance. Doses in the range 500 mg-1 g hourly for 14-21 days are usual.

With cotrimoxazole the clinical response is at least as rapid as with chloramphenicol.

The dose is two tablets 8-hourly until afebrile, then two tablets 12-hourly for 10 days.

Relapses after chemotherapy occur in a variable proportion of patients (2-10%), are usually rather less severe than the initial illness, and respond to the same chemotherapy.

### Carrier state.

This commonly persists for some months into convalescence, and when it terminates spontaneously such patients are called convalescent carriers. They are an obvious source of infection to others, but even more important are chronic carriers (1-3% of cases) in which a persisting focus of infection smoulders on in the gallbladder (faecal carriers) or urinary tract (urinary carriers). In most endemic areas few carriers are identified, because culture facilities do not exist. Persistent elevation of Vi antibodies often accompanies the carrier state.

Chronic carriers may, when employed as food-handlers, cause hundreds of cases and many deaths. Chronic faecal carriers usually have chronic cholecystitis with or without gallstones, and there are often pathological abnormalities in the urinary tract, including *Schistosoma haematobium* infection in chronic urinary carriers.

Chronic carriers are usually treated with Cotrimoxazol, two tablets twice a day for 3 months. That is the most cost-effective treatment. Ampicillin and amoxycillin in high dosage for the same length of time, combined with probenecid, may also be effective. But faecal carriers with gallstones only respond temporarily to chemotherapy and cholecystectomy is needed to terminate the carrier state in such cases.

Recently, norfloxacin at a dose of 400 mg twice daily for 28 days was shown to cure 11 of 12 carriers.

If the patient is intelligent and conscientious, and not a food-handler, the carrier state need not be treated at all, for the fastidious maintenance of high standards of environmental and personal hygiene will prevent transmission of the infection to others.

### Typhoid vaccine

A monovalent vaccine using killed *S. typhi* organisms is most widely used. The old typhoid and paratyphoid vaccine A and B (TAB) contained paratyphoid organisms also but was never proved to provide worthwhile immunity to the paratyphoids, and often produced more severe reactions than the monovalent vaccine. A modern purified surface antigen vaccine is now in use, but is very expensive. The live attenuated oral vaccine requires three doses to provide 1 year's immunity.

The degree of protection given by the vaccine is about 90%. If typhoid does develop in a vaccinated subject, it is no less severe than in the unvaccinated.

# TUBERCULOSIS IN THE TROPICS

## **Historical aspects**

During the course of the 20<sup>th</sup> century the dramatic decline in the incidence of tuberculosis (TB) in industrialized countries was primarily due to improved socio-economic conditions.

The chances of achieving successful cure in an individual with active TB remained low until the discovery of effective antituberculous drugs: streptomycin in 1946, isoniazid in 1952, pyrazinamide in 1954 and rifampicin in 1970.

## **Epidemiology**

### Size of the problem

There are estimated to be 8-10 million new TB cases diagnosed in the world each year and the disease is responsible for the death of 2-3 million people annually. The bulk of this morbidity and mortality occurs in tropical and subtropical regions where infection rates approach 2-3% per year of life. The incidence of TB is actually increasing, so that there are more new cases now than 20 years ago. The single most important factor in the resurgence of TB is the AIDS pandemic, as infection with HIV greatly increases the risk of TB infection and disease.

### Transmission

Infection with the tubercle bacillus is by inhalation of droplet nuclei, which have been coughed up by someone with active pulmonary disease. This is the only way that infection with *Mycobacterium tuberculosis* can occur. A sputum-smear-positive individual is 10 times more infectious than someone who is smear-negative, so the emphasis of TB control in the tropics should remain the detection of these infectious individuals, even in the presence of high HIV seroprevalence.

### Risk of progression to disease

Up to 15% infected people develop the disease – 5% within 2 years of infection, 5% within 5 years and the rest during the remainder of their lifetime.

Factors, which influence infection and progression, include:

1. Intensity of exposure: overcrowding.
2. Age: very young and very old.
3. Genetic susceptibility: weak association with human leucocyte antigen (HLA) type
4. Immunosuppression: HIV, malnutrition, transplant recipients.
5. Trauma: TB osteomyelitis
6. Miscellaneous: alcohol.

## **Pulmonary tuberculosis**

Pulmonary TB usually presents with chronic cough with blood-stained sputum, weight loss, fevers and sweats. Clinical examination is often unhelpful but most patients will be malnourished and some will have finger clubbing or focal signs in the chest. The single most important investigation is a sputum smear to look for acid-fast bacilli (AFB). The best quality sputum samples are obtained in the morning and should be stained using the Ziehl-Neelsen method and examined under oil immersion using a light microscope. Fluorescent microscopy is quicker but expensive and is appropriate only in centres where large numbers of samples are processed. Culturing the sputum of smear-positive individuals for mycobacterium is not routinely required as it is expensive and plays little part in controlling the transmission of the disease.

The chest X-ray changes of pulmonary TB are most often in the apices with consolidation and cavitation.

The differential diagnosis includes lung abscess, pulmonary paragonimiasis, nocardiosis, actinomycosis, histoplasmosis, melioidosis and bronchial carcinoma and, although these are all much less common than TB, one must be wary of diagnosing the disease on the basis of a chest X-ray alone.

Enormous research effort has gone into finding alternative methods for diagnosing TB, but for pulmonary disease none have yet to supersede sputum microscopy. Serodiagnosis using monoclonal antibodies or PCR to detect mycobacterial DNA may find a place in extrapulmonary or paucibacillary disease and DNA fingerprinting is proving to be a superb epidemiological tool with which to study the transmission of *Mycobacterium tuberculosis* in human populations. However, examining sputum smears will remain the cornerstone of TB control in the tropics for the foreseeable future.

### **Tuberculous meningitis**

The clinical presentation of tuberculous meningitis is very variable, ranging from headache, fever and behavioural changes to convulsions and deep coma. Arachnoiditis affecting the brainstem may cause cranial nerve palsies or a polyradiculopathy if it involves the spinal nerve roots. Most patients will have a stiff neck and lumbar puncture is mandatory. Typical CSF findings are a lymphocyte pleocytosis, elevated protein and low glucose. Staining the CSF for AFB will confirm the diagnosis in only 25% of cases and polymorphs may outnumber lymphocytes early in the disease. A high index of suspicion is therefore required and treatment may have to be commenced without a definitive diagnosis. The main differential diagnosis are partially treated bacterial meningitis, viral meningitis and cryptococcal meningitis.

### **Bone and joint tuberculosis**

TB of the spine is the commonest cause of paraplegia in the tropics. It affects the thoracic more often than the lumbar spine and causes a characteristic gibbus deformity due to collapsed vertebral bodies.

Joint TB is usually monoarticular, affecting the hip or knee, and should be suspected in any patient with a chronic painful large joint. Diagnosis is usually obvious on X-ray.

### **Genitourinary tuberculosis**

Renal TB should be suspected in any patient with chronic dysuria and frequency of micturition who fails to respond to standard antibiotics. The urine is abnormal in 90% of cases, namely a sterile pyuria often with microscopic haematuria. Microscopy for AFB is unreliable and usually negative, so early-morning urine should be cultured for TB if facilities are available. Plain abdominal X-ray may show renal or ureteric calcification and intravenous pyelography is usually abnormal with caliceal irregularities or hydronephrosis.

TB of the male genital tract presents with scrotal masses, which may discharge on to the surface. It often coexists with renal TB. In females the disease presents as infertility or with symptoms of pelvic inflammatory disease.

### **Gastrointestinal and abdominal tuberculosis**

TB can affect the gastrointestinal tract anywhere from mouth to anus and can be very difficult to diagnose. It most often causes disease in the ileocaecal region and presents with abdominal pain, fever and diarrhoea. Stricture formation is common and may cause intermittent subacute obstruction. A stricture may be visible on plain abdominal X-ray but

useful by allowing inspection of the abdominal cavity and biopsy of suspicious areas under direct vision.

### **Tuberculosis and HIV**

There is a major interaction between *M. tuberculosis* and HIV, causing a huge public health problem in poor tropical countries where infection with both agents is common. The most obvious manifestation of this is the rising incidence of all forms of TB in tropical Africa, so that many more people are requiring antituberculous treatment. Up to half of these cases are HIV-positive.

The clinical implications are both diagnostic and therapeutic. Many HIV-positive patients with TB will present in the same way as those who are HIV-negative, but there is a tendency for more sputum-smear-negative disease with less cavitation, more lymphatic disease and more extrapulmonary disease, especially pleural and pericardial. Active TB can occur at any stage of HIV infection, not only in the profoundly immunosuppressed.

The principles of treatment are similar in HIV-positive patients and the initial response is often very good. Overall mortality is increased, but this is due to infections other than TB, such as severe pneumococcal or *Salmonella* bacteraemias. The recurrence rate following treatment may be increased; this is often due to reinfection rather than true relapse.

There is an increased incidence of severe cutaneous hypersensitivity reactions to drugs – especially with thiacetazone – which can be life threatening.

The role of primary and secondary antituberculous chemoprophylaxis in HIV positive individuals is an area of controversy and intense debate at the present time.

### **Chemotherapy for tuberculosis**

#### Basic principles

Wherever possible, use a regimen shown to be effective in controlled trials and emphasize the importance of continuing treatment for the prescribed duration. Infectiousness disappears within 2 weeks, symptoms disappear within 4 weeks and sputum should be smear-negative within 2-3 months. Compliance will be impossible to achieve if the drugs are not supplied free of charge. If there is a national TB control programme in operation you must notify the patient to the programme.

The essential antituberculous drugs (with abbreviation) are **Isoniazid (H), Rifampicin (R), Streptomycin (S), Pyrazinamide (Z), Thiacetazone (T), Ethambutol (E)**.

#### Drug regimens

Regimens are an initial intensive phase followed by a longer maintenance phase. The choice of combination and the total duration of therapy depend essentially on availability. The longer non-rifampicin-containing regimens are sometimes called standard chemotherapy and the shorter-duration combinations, which include rifampicin, are called short-course chemotherapy. The latter should be used wherever possible, as cure rates are much higher and so more cost-effective. Isoniazid is always given for the duration of therapy and regimens, which do not include rifampicin in the intensive phase but not the maintenance phase, require 8 months' duration. Regimens of 6 months' duration must include pyrazinamide for the first 2 months and rifampicin for the whole 6 months. Thiacetazone should be avoided unless the patient is known to be HIV-negative.

In extrapulmonary disease the duration of therapy is the same, except in meningitis when the maintenance phase has to be prolonged to 18 months.

Toxicity of regimens containing thiacetazone is much higher in those who are HIV-positive.

# CHOLERA

## Introduction

Cholera is an acute diarrhoeal disease caused by the gram negative bacillus *Vibrio cholerae*. Although more than 100 serogroups exist, only two cause human disease: *V. cholerae* O1, of which there are two biotypes (Classical and El Tor) and *V. cholerae* O139 which emerged in 1992. Cholera is known to cause worldwide pandemics. *V. cholerae* O1, biotype El Tor accounts for most cases in the current, seventh pandemic, although serogroups O139 and O1 (Classical biotype) are present in India and Bangladesh. The O139 epidemic has been occurring in populations assumed to be largely immune to *V. cholerae* O1 and has rapidly spread to many countries including the United States

*V. cholerae* is endemic in many resource-poor countries, particularly in areas of inadequate sanitation and food hygiene practices. Man is the only known host of cholera.

## ETIOLOGY

*V. cholerae* are short (0.2 to 0.4  $\mu\text{m}$  by 1.5 to 4.0  $\mu\text{m}$ ), slightly curved gram-negative rods that are readily seen in Gram-stained smears of the watery excreta of patients with cholera. *V. cholerae* grows rapidly on a number of selective media, including bile-salt agar, glycerin-tellurite-taurocholate agar, and thiosulfate- citrate-bile-salt-sucrose (TCBS) agar. Of these, TCBS agar has the advantage of not requiring sterilisation before use. On TCBS agar, vibrios can be distinguished from other enteric microorganisms by a distinct, opaque yellow colonial appearance. Distinction between the two major serotypes -Inaba and Ogawa- is made by slide agglutination with type-specific antisera. Identification of the El Tor biotype is important for epidemiologic purposes; it is distinguished from the classic biotype by its resistance to polymyxin B and by its ability to cause hemolysis of sheep erythrocytes.

## EPIDEMIOLOGY

### History and spread of epidemic cholera

Cholera has smoldered in an endemic fashion on the Indian subcontinent for centuries. There are references to deaths due to dehydrating diarrhea dating back to Hippocrates and Sanskrit writings. Epidemic cholera was described in 1563 by Garcia del Huerto, a Portuguese physician at Goa, India. The mode of transmission of cholera by water was proven in 1849 by John Snow, a London physician. In 1883, Robert Koch successfully isolated the cholera vibrio from the intestinal discharges of cholera patients and proved conclusively that it was the agent of the disease.

Cholera has always been endemic in India and Bangladesh, in the huge delta formed by the confluence of the Ganges, Brahmaputra, Jamuna and Meghna rivers. Probably there was no cholera in Europe or America before the 19<sup>th</sup> century. Between 1817 and 1923 there were various great pandemics, probably caused by the classic *V. cholerae* (there is no certainty as to the exact strain). The first pandemic which started in 1817 did not reach Western Europe. In 1829 the bacterium was introduced into the countries around the Persian Gulf via a British army unit stationed in India. From Iran the infection spread to Iraq, Syria, Georgia and Astrakhan (north of the Black Sea). It then travelled towards Odessa, Moscow, Vienna, Warsaw and Hamburg reaching England via the port of Sunderland. The first cases in London were seen in February 1832. The third pandemic merged with the second and was amplified by the miserable conditions during the Crimean war. The pathogen was discovered in 1884 by Robert Koch during the fifth pandemic (first work in 1883 in Alexandria, Egypt,

confirmation followed by research in India in 1884, with isolation of the bacterium in culture). In fact the bacterium had already been described in 1849 by Pouchet and in 1854 by Filippo Pacini, an Italian physician. However, the latter's work on this was not known outside Italy (he was known abroad due to his description of Pacini's corpuscles, the pressure receptors in the skin). The germ theory and in particular the work of Koch were attacked by Pettenkorfer and his student Emmerich, who each drank a vial filled with bacteria as proof against the role of *V. cholerae*. Amazingly, Pettenkorfer did not then get cholera, but Emmerich suffered severe diarrhoea for 48 hours. When each pandemic began and ended is rather unclear.

<b>Cholera pandemics since 1817</b>			
<b>Number</b>	<b>Years</b>	<b>Origin</b>	<b>Pathogen</b>
1	1817-1823	India	?
2	1829-1851	India	?
3	1852-1859	India	?
4	1863-1879	India	?
5	1881-1896	India	<i>V. cholerae</i> O1, classic
6	1899 -1923	India	<i>V. cholerae</i> O1, classic
7	1961 to present	Sulawesi	<i>V. cholerae</i> O1, El Tor
8	1992 to present	Madras, India	<i>V. cholerae</i> O139

After the sixth pandemic there was a strange silence for about 40 years, for which no good explanation exists. The seventh pandemic was caused by El Tor. It started in 1961 in Celebes (Sulawesi), Indonesia, reached India in 1964 and Africa in 1970. There are several characteristics of the El Tor strain that confer upon it a high degree of "epidemic virulence" allowing it to spread across the world as previous strains have done. First, the ratio of cases to carriers is much less than in cholera due to classic biotypes (1: 30-100 for El Tor vs. 1: 2 - 4 for "classic" biotypes). Second, the duration of carriage after infection is longer for the El Tor strain than the classic strains. Third, the El Tor strain survives for longer periods in the extraintestinal environment.

In 2 years the infection passed through 29 African countries. In 1973 it arrived in the Gulf of Mexico. Early in 1991 the infection spread rapidly in Peru. In 3 weeks there were 30,000 cases. The bacterium then spread further into South America, causing 360,000 cases within the year. In the summer of 1992 a second, less severe outbreak occurred. Nevertheless by August 1992 "only" 5,000 deaths had been reported (from an estimated total of 600,000 cases), thanks to the wide-spread use of rehydration therapies. The case-fatality ratio varied depending on the region. After 1993 the disease assumed an endemic character in several countries, sometimes with local outbreaks. At the end of 1993 the cumulative total amounted to 900,000 cases in three years (1991-1993), with a cumulative mortality of 8,000. According to one hypothesis cholera bacteria infected the marine plankton off the Peruvian coast via the ballast water from a Chinese freighter. The possible role of changes in the nutrient-rich von Humboldt current is still unclear.

About 80% of the cholera in 1997 occurred in Africa, chiefly in the horn of Africa (118,000 cases were reported officially). The increase in cholera in this region followed heavy rains and flooding (possibly associated with the El Niño weather phenomenon).

Since 1992 *V. cholerae* O139 is recognised as a cause of a disease which is clinically identical to classic cholera, but which also occurs frequently in adults. Classic cholera in India, on the other hand, is common in children. There is no cross immunity with *V. cholerae* O1. Bacteria of the O139 serogroup have a polysaccharide capsule (unlike *V. cholerae* O1), which may explain the increased risk of septicaemia. In the following years this new serogroup spread across Bangladesh, India, Pakistan and Southeast Asia. By the end of March 1993 more than 100,000 cases had been reported in Bangladesh. If further spread continues, as with the earlier epidemics, it will be possible to refer to this as the beginning of the eighth pandemic. It was observed in India that, after the first spread of *V. cholerae* O139, new variants (clones) of *V. cholerae* O1 El Tor once more gained the upper hand. Cholera also surfaces regularly in Madagascar. From the beginning of December 1999 until the end of February 2000 more than 12,400 cases were reported. The disease can thus certainly not be regarded as an entity which only existed "in the past".

Humans are the only documented natural host and victim of *V. cholerae*. Cholera is transmitted through the faecal-oral route, most commonly by consumption of contaminated water and to a lesser degree food; direct person-to-person transmission is rare. A high infecting dose (as many as 10<sup>11</sup> organisms) is required to cause illness in healthy individuals.

Water clearly plays a major role in the transmission of *V. cholerae* in endemic rural areas. During major epidemics, however, the direct contamination of food with infected excreta is also important. Persons with mild or asymptomatic infections (contact carriers) probably play an important role in the dissemination of epidemic disease. The ratio of persons with asymptomatic infection to those with clinical disease varies from 4:1 to more than 20:1 in different outbreaks. A prolonged gallbladder carrier state may develop in up to 3% of patients convalescing from cholera caused by the El Tor biotype. The gallbladder carrier state has never been observed in the pediatric age-group. The role of such convalescent carriers in the transmission of the disease is not known. In the endemic areas of Bangladesh and West Bengal, cholera is predominantly a disease of children; attack rates are 10 times greater in the 1- to 5-year age-group than in the those over the age of 14 years. However, when the disease spreads to previously uninvolved regions, the attack rates are initially at least as high in adults as in children.

## **PATHOGENESIS AND PATHOLOGY**

All signs, symptoms, and metabolic derangements in cholera result from the rapid loss of liquid from the gut. In adults with cholera, the feces are nearly isotonic with plasma. As compared with plasma, the concentrations of sodium and chloride are slightly less, bicarbonate is approximately twice as high, and potassium is three to five times higher. The increased electrolyte secretion is caused, in the absence of morphologic damage to the gut mucosa, by a protein enterotoxin that is elaborated by all pathogenic strains of *V. cholerae*. The enterotoxin has a molecular mass of 84,000 daltons and consists of a binding (B) moiety and an activating (A) moiety. Five equal sub-units with a molecular weight of 11,500 each make up the B moiety. On exposure to small bowel epithelial cells, each B subunit rapidly binds to GM<sub>1</sub> monosialoganglioside in the gut cell wall.

Following binding, the A moiety (composed of two unequal subunits) migrates through the epithelial cell membrane. The A<sub>1</sub> subunit (molecular weight about 23,000)

contains adenosine diphosphate (ADP) -ribosyltransferase activity and stimulates, by a catalytic process, the transfer of ADP-ribose from nicotinic acid adenine dinucleotide (NAD) to a guanosine triphosphate (GTP) -binding protein that regulates adenylate cyclase activity. The ADP ribosylation of the GTP binding protein inhibits the GTP turnover reaction and causes a sustained increase in adenylate cyclase activity. The resultant increased intracellular cyclic adenosine 5' monophosphate (cyclic AMP) acts at two sites to cause net secretion of isotonic liquid within the small bowel lumen. The increased cyclic AMP inhibits neutral sodium chloride absorption across the brush border via the cotransport mechanism; it also stimulates active chloride secretion into the gut lumen. Cyclic AMP apparently exerts a direct chloride secretory action primarily on crypt cells and inhibits neutral sodium chloride absorption primarily in cells of the villus. The net effect of the increased cyclic AMP is the secretion of isotonic liquid by all segments of the small bowel, at a rate that exceeds the absorptive capacity of the colon. The resultant isotonic, watery feces represent the sum of the secretions of all segments of the small bowel, slightly modified during passage through the colon.

## MANIFESTATIONS

The clinical onset of cholera (following a usual incubation period of 6-72 hours) is generally that of abrupt, painless, watery diarrhea. In severe cases, several liters of liquid may be lost within a few hours, rapidly leading to profound shock. At varying intervals after the onset of diarrhea, vomiting may ensue. This is characteristically effortless and is not preceded by nausea. In the more severe cases, muscle cramps are almost invariably present and commonly involve the calves.

When first seen by the physician, the patient who is severely ill with cholera is cyanotic and has sunken eyes and cheeks, a scaphoid abdomen, poor skin turgor, and thready or absent peripheral pulses. The voice is high pitched or inaudible; the vital signs include tachycardia, tachypnea, and low or unobtainable blood pressure. The heart sounds are distant and often inaudible, and bowel sounds are usually hypoactive. Major alterations in mental status are not common in adults; the patient usually remains well oriented, though apathetic, even in the face of severe hypovolemic shock. As many as 10% of small children may have central nervous system abnormalities that range from stupor to convulsions. In all epidemics, there are large numbers of mild cases in which the loss of liquid from the gut is not severe enough to require hospitalisation.

The loss of liquid and electrolytes continues for 1 to 7 days, and subsequent manifestations depend on the adequacy of replacement therapy. With prompt replacement, physiologic recovery is remarkably rapid and uniform despite continuing voluminous diarrhea. If therapy is inadequate, the mortality rate in hospitalized patients may exceed 50%. The important causes of death are hypovolemic shock, uncompensated metabolic acidosis, and uremia. When renal failure occurs, the characteristic pathologic findings are those of acute tubular necrosis secondary to prolonged hypotension.

In endemic or epidemic areas, the working diagnosis of cholera should be made on the basis of the clinical picture. Liquid and electrolyte replacement therapy should be instituted immediately. Although a cholera-like illness may be caused by microorganisms other than *V. cholerae*-most frequently by enterotoxigenic *Escherichia coli* - the resulting physiologic and metabolic abnormalities are the same, so that identical intravenous and peroral electrolyte therapy should be used in all such cases.

Diagnostic culture techniques are relatively simple. A reliable and practical method consists of direct plating of feces on TCBS agar. Typical opaque yellow colonies appear in 18 hours. Final identification requires agglutination with group- and type-specific antisera and

the demonstration of characteristic biochemical reactions. Rapid, tentative diagnosis may be made by the direct darkfield microscopic observation of the characteristically rapid motility of the comma-shaped bacilli in fresh feces. Group- and type-specific antisera immobilize homologous strains and clearly distinguish them from other vibrios.

With adequate therapy, the mortality rate approaches zero. Largely because of the mechanical problems inherent in the administration of large amounts of liquid to small children, their mortality rate still remains at 1% to 2% despite the best current therapy. A single attack of cholera confers protection against subsequent infection by the same serotype of *V. cholerae* for several years.

## **THERAPY**

Successful therapy demands only prompt replacement of gastrointestinal losses of liquid and electrolytes. Of the several appropriate commercial preparations, lactated Ringer's solution is the most widely available. This isotonic liquid should be given rapidly by IV injection—50 ml to 100 ml per minute—until a strong radial pulse is restored. Subsequently, the same solution should be infused in quantities equal to gastrointestinal losses or, if these losses cannot be measured accurately, at a rate sufficient to maintain a normal radial pulse volume and normal skin turgor. Overhydration can be avoided by careful observation of the veins in the neck and by auscultation of the lungs. Close observation of the patient is mandatory during the acute phase of the illness. An adult patient can lose as much as 1 liter per hour of isotonic liquid during the first 24 hours of the disease. Inadequate or delayed restoration of electrolyte losses results in a very high incidence of acute renal insufficiency. Serious hypokalemia is rare in adults, and potassium replacement may usually be carried out by giving approximately 15 mEq of potassium chloride PO for each liter of feces that is produced.

In children, complications are both more frequent and more severe. The most serious include stupor, coma, and convulsions (unique to pediatric patients); pulmonary edema and cardiac arrhythmias may occasionally lead to cardiac arrest. The central nervous system complications may be due to hypoglycemia (observed only in pediatric patients), hyponatremia resulting from the administration of isotonic solutions to the pediatric patient (who, unlike the adult patient, produces feces with a sodium concentration significantly less than is present in plasma), or cerebral edema—presumably secondary to rapid shifts of liquid during intravenous administration. Pulmonary edema may result if liquid is given intravenously at too rapid a rate, especially in the presence of severe metabolic acidosis. Cardiac arrhythmias may result from potassium depletion in children but occur rarely in adults with cholera. Each of these complications can be avoided by the careful intravenous administration of solutions especially designed to replace the fecal electrolyte losses of children with cholera.

Lactated Ringer's solution is also satisfactory in children but should be supplemented by peroral administration of water and glucose; one glass (240 ml) of 5% glucose should be given PO, every 6 hours, to children who are receiving lactated Ringer's solution by intravenous injection. The intravenous administration of this solution must be carefully monitored, with frequent auscultation of the lungs and inspection of venous filling in the neck in order to avoid over-hydration.

Peroral replacement of water and electrolytes is effective in almost all patients who are alert. Glucose-electrolyte solutions may be given perorally in mild cholera throughout the course of illness. Early peroral therapy prevents serious depletion of electrolytes in all except the most severe (2% to 4%) cases of cholera. In the most severe cases, the initial hypovolemic shock must be corrected by initial, rapid intravenous treatment. Losses from the gut

may be replaced by peroral administration of an isotonic solution prepared by adding 20 g glucose, 3.5 g sodium chloride, 2.5 g sodium bicarbonate, and 1.5 g potassium chloride to a liter of water (yield, in mEq/liter: sodium, 90; potassium, 20; chloride, 80; bicarbonate, 30; glucose, 111). Glucose is an essential component of this solution because the uptake of sodium in the small bowel is enhanced by the presence of intraluminal glucose. If glucose is not available, sucrose (table sugar) may be substituted in a concentration of 40 g/liter; in the small bowel, sucrase splits sucrose into glucose and fructose; that is, half of the sucrose becomes available to facilitate the absorption of sodium. Liquids are initially given perorally in large quantities (e.g., 250 ml every 15 minutes in adults) until balance has been restored, as gauged by clinical observations. Thereafter, sufficient quantities are administered to balance the output of feces: 1.5 liters of glucose-electrolyte solution should be given PO for each liter of feces. The peroral administration of liquids does not decrease the volume of liquid lost through the gut, but provides replacement to counterbalance the enterotoxin-induced secretion of liquid.

Provision of adequate liquid with correction of the attendant biochemical derangements results in rapid recovery in virtually all patients with cholera. However, adjunctive treatment with antimicrobics dramatically reduces the duration and volume of diarrhea and results in the early eradication of vibrios from the feces. Tetracycline in a dose of 30 mg to 40 mg/kg body wt/day, PO, as four equal portions, every 6 hours, for 2 days was once uniformly successful. However, since 1979, a number of isolates of *V. cholerae* from patients in Bangladesh and Tanzania have exhibited resistance to tetracycline. That phenomenon is now emerging. Tetracycline resistant strains are now treated with Cotrimoxazole, erythromycin, doxycycline, furazolidone and chloramphenicol

A cholera vaccine is available, but is normally not recommended by the CDC or the World Health Organization because only 50 to 70 percent of those who take the vaccine develop immunity to cholera, and the immunity lasts only a few months. Currently, no country requires the cholera vaccine for entry if arriving from cholera-infected countries.

## **EPIDEMIC CONTROL AND PREVENTIVE MEASURES**

When cholera appears in a community it is essential to ensure three things: hygienic disposal of human faeces, an adequate supply of safe drinking water, and good food hygiene. Effective food hygiene measures include cooking food thoroughly and eating it while still hot; preventing cooked foods from being contaminated by contact with raw foods, including water and ice, contaminated surfaces or flies; and avoiding raw fruits or vegetables unless they are first peeled. Washing hands after defecation, and particularly before contact with food or drinking water, is equally important.

Routine treatment of a community with antibiotics, or "mass chemoprophylaxis", has no effect on the spread of cholera, nor does restricting travel and trade between countries or between different regions of a country. Setting up a *cordon sanitaire* at frontiers uses personnel and resources that should be devoted to effective control measures, and hampers collaboration between institutions and countries that should unite their efforts to combat cholera.

Limited stocks of two oral cholera vaccines that provide high-level protection for several months against cholera caused by *V. cholerae* O1 have recently become available in a few countries. Both are suitable for use by travellers but they have not yet been used on a large scale for public health purposes. Use of this vaccine to prevent or control cholera

outbreaks is not recommended because it may give a false sense of security to vaccinated subjects and to health authorities, who may then neglect more effective measures.

In 1973 the WHO World Health Assembly deleted from the International Health Regulations the requirement for presentation of a cholera vaccination certificate. Today, no country requires proof of cholera vaccination as a condition for entry, and the International Certificate of Vaccination no longer provides a specific space for recording cholera vaccinations.

## AMEBIASIS

Amebiasis is a protozoan infection caused by *Entamoeba histolytica* and is the third most common cause of mortality among parasitic infections after malaria and schistosomiasis. Approximately 1% of the world's population is thought to be infected, with 40,000–110,000 related deaths reported annually. Although distributed worldwide, amebiasis is most frequently seen among the lower socioeconomic classes in tropical and subtropical climates. The infection is acquired by ingestion of cysts that become trophozoites in the colon and may invade the bowel wall

*Entamoeba histolytica* was probably a major cause of illness in humans in ancient times. However, it was not recognised as the cause of amebiasis until the late 1800s when Kartulis (1886) found amebae in the feces of 150 patients with dysentery but none in feces from controls, and Hlava (1887) produced diarrheal disease in kittens using ameba-positive feces from a study of 60 patients with dysentery. After observing amebae in pus from a hepatic abscess in 1890, Osler encouraged study of amebic disease at Johns Hopkins with the result of publication in 1891 of Councilman and Lafleur's monograph describing the pathology of amebiasis. In addition to introducing the terms "amebic dysentery" and "amebic abscess of the liver," this work noted the importance of amebic ingestion of erythrocytes and the presence of flask-shaped ulcers of the colon. In 1911, Walker showed that *E. histolytica* was separable from *Entamoeba coli* by morphologic characteristics. Studying volunteers, he proved that the cysts of *E. histolytica* are infective but that *E. coli* does not cause disease and confirmed the utility of emetine as an amebicidal agent.

### ETIOLOGY

The subphylum Sarcodina is characterized by motility dependent on pseudopods; *E. histolytica* differ from the other ameba in this group by the presence of ingested erythrocytes and pathogenic potential for humans. The question about why some strains of *E. histolytica* are invasive and others appear to be noninvasive commensals has been debated. Some investigators claim that the trophozoites of invasive strains are larger, but others believe that size is not a factor. Antigenic and isoenzyme analysis may prove to be helpful in defining differences in virulence.

The trophozoites are 10  $\mu\text{m}$  to 60  $\mu\text{m}$  in diameter and have fine cytoplasm, and the nucleus contains a central karyosome. A definitive identification can only be made by less-experienced observers by identifying ingested erythrocytes in the rapidly motile trophozoites of *E. histolytica*. The cysts contain one to four nuclei, a large glycogen vacuole, and rod-shaped, smooth chromatoidal bodies 10  $\mu\text{m}$  to 20  $\mu\text{m}$  in size.

*Entamoeba coli*, *Entamoeba hartmanni*, *Entamoeba polecki*, *Endolimax nana*, and *Iodamoeba buetschlii* are nonpathogenic amebae that may be found in the feces of humans in the United States. They have not been associated with disease in humans.

## EPIDEMIOLOGY

The epidemiology of *E. histolytica* as determined by examining feces is complicated by the low yield of positive examinations from a single specimen, even from persons known to be infected. Serologic surveys are more likely to indicate invasive disease, and positive titers may persist long after the infection has resolved. All populations of the world are infected with *E. histolytica*; the local rates of fecal positivity of 1% to 69% correspond to over 10,000,000 cases a year, with 30,000 to 40,000 deaths. Tropical and subtropical populations have a higher prevalence, but poor sanitary conditions in any climate may be associated with a high incidence of disease. Studies in the United States yield an incidence of 1% to 5%. The organism is endemic in orphanages, mental institutions, southern rural areas, and areas of substandard housing. Homosexuals are at an increased risk of acquiring amebiasis, as well as giardiasis, cryptosporidiosis, and bacterial dysentery. The patient with acquired immunodeficiency syndrome (AIDS) is not only more likely to have amebiasis but also is more likely to have invasive disease and be unable to resolve the infection.

The life cycle of *E. histolytica* involves a trophozoite stage and a cystic stage. The trophozoites are found in the intestinal tract of the host except when they become invasive. The encystment of the trophozoites is stimulated by unidentified factors in the fecal stream. Ingestion of the cysts of *E. histolytica* is responsible for the transmission of infection from infected to uninfected persons. The transmission may be by direct fecal-oral contact or through fecal contamination of water and vegetables. The cockroach and housefly may be implicated indirectly as a means of transmission, because cysts pass unharmed through their guts. Trophozoites cannot survive outside the intestinal tract and are therefore not generally involved in transmission of illness.

## PATHOGENESIS AND PATHOLOGY

The virulence of different isolates, and even the same isolate, may differ markedly between hosts. Amebae repeatedly passed through cultures may lose invasiveness in weanling rats. Strains causing disease in humans are initially more invasive in rats than strains not associated with disease. There is also a good correlation with positive serology and virulence in rats. The cytolytic action of amebae is dependent on adherence to the host's cells. Adherence is mediated by several amebic receptors and the flux of intracellular calcium. The exact nature of these factors is still unknown. A relationship between bacterial flora, iron, and cholesterol to the virulence of amebae has been suggested but is probably only of minor importance.

Although almost every organ and system may be infected by *E. histolytica*, the major lesions are colonic ulcers, colonic granulomas, diffuse hepatitis, hepatic abscess, pulmonary abscess, brain abscess, and rectal ulcerations. The primary lesions of the intestinal tract are ulcerations in the cecum, appendix, and adjacent ascending colon. The process starts within 24 hours after the ingestion of cysts in experimental infections of kittens or weanling rats. The amebae are first seen in the crypts and exhibit a superficial lytic action and necrosis of the epithelial cells. As they multiply, they penetrate along the base of the glands and enter the interstitial tissues between the gland cells. They then advance to be halted at the muscularis mucosae, a relatively resistant barrier. At this stage, the ulcer is a pinhead lesion as seen from the lumen. If the muscularis is breached, they spread to the nonresistant submucosa and fan out radially, forming the characteristic flask-shaped ulcer. The lesions enlarge, gradually losing their characteristic form, and develop elevated margins with a white exudate on the base of the ulcer. From this lesion, they may penetrate into venules and lymphatics or into the peritoneal cavity and may disseminate to other organs.

The normal peristaltic action of the intestine milks the progeny of the amebae in the initial ulcerations out into the lumen of the gut. This spreads the organism throughout the colon and into the fecal stream, where some trophozoites encyst and are passed in the feces. With massive infection, a firm, fibrous, nodular lesion in the colon may form. Termed amebic granuloma, the lesion is easily confused with carcinoma on barium contrast roentgenography.

Trophozoites that penetrate into the mesenteric venules are carried to the liver via the portal vein. Many fail to lodge in the liver and are destroyed by the immune system or lodge in other organs, where they may cause disease. Those caught in the hepatic microcirculation produce necrosis of the endothelium and penetrate into the periportal sinusoids, where they may digest pathways into the hepatic lobules. There initially is no inflammatory reaction because of lysis of the reactive cells that come in contact with trophozoites. As necrosis progresses, however, polymorphonuclear leukocytes gradually surround the lesion without formation of a definite wall. The lesions may remain focal or may progress to form large, solitary abscesses.

Pulmonary involvement occurs either by direct hematogenous spread or by penetration from a ruptured hepatic abscess. The lesion is similar to a hepatic abscess with little inflammatory reaction.

Brain abscesses differ little from hepatic and pulmonary lesions except for their more rapid progression to death. Amebic skin lesions take the form of ulcerations of the perirectal tissues, superficially resembling bacterial and traumatic ulcerations; there is little inflammatory reaction in the absence of secondary infection.

## MANIFESTATIONS

**History:** The signs and symptoms of amebic liver abscess often are nonspecific, resembling those of pyogenic liver abscess or other febrile diseases.

The incubation period for amebiasis is usually 1 to 5 days but may vary from 1 day to 1 year. The disease begins with a prodromal episode of diarrhea, abdominal cramps, nausea, vomiting, and tenesmus; there may be vague abdominal discomfort, general malaise, loss of appetite, loss of weight, and mental apathy. The feces may be watery or formed, but with dysentery, they are generally watery, containing mucus and blood.

On average, about one in 10 people who are infected with *E. histolytica* becomes sick from the infection.

### Time of onset

- Patients with amebic liver abscess usually present acutely (duration of symptoms <14 d), with the most frequent complaints being fever and abdominal pain. This presentation is characteristic of younger patients.
- The subacute presentation mostly is characterized by weight loss, and, in less than half the cases, abdominal pain and fever are present.

### Abdominal pain

- Abdominal pain is the most common element in the history and is present in 90-93% of patients.
- The pain most frequently is located in the right upper quadrant (54-67%) and may radiate to the right shoulder or scapular area.
- Pain increases with coughing, walking, and deep breathing, and it increases when patients rest on their right side.
- The pain usually is constant, dull, and aching.

### Constitutional symptoms

- Fever is present in 87-100% of cases.

- Rigors are present in 36-69% of cases.
- Nausea and vomiting are present in 32-85% of cases.
- Weight loss is present in 33-64% of cases.

#### Diarrhea

- Diarrhea is present in less than one third of patients at the time of diagnosis.
- Some patients describe a history of having had dysentery within the previous few months.
- Bloody diarrhea is present in 7% of cases.

#### Pulmonary symptoms

- Pulmonary symptoms are present in 18-26% of cases.
- The most frequent symptoms are cough and chest pain, which may represent a sign of secondary pulmonary involvement by abscess rupture in the pleural cavity.
- When coughing produces an odorless brown substance similar to anchovy paste, a bronchopleural fistula has developed.

#### Recent travel to endemic areas

- Onset of symptoms usually occurs within 8-12 weeks from the date of travel.
- In 95% of cases, onset occurs within 5 months of returning from travel to an endemic area.
- A remote travel history of as many as 12 years has been reported.

#### **Physical:**

- Fever is the most common sign and is found in as many as 99% of cases.
- Hepatomegaly is present in some cases.
- The frequency varies widely in different series published, reporting as high as 63% in one series and as low as 18% in another.
- Hepatomegaly with pain upon palpation is one of the most important signs of amebic liver abscess.
- Point tenderness over the liver, below the ribs, or in the intercostal spaces is a typical finding.

#### Abdominal tenderness

- In 55-75% of cases, abdominal tenderness is located in the right upper abdominal quadrant.
- When the abscess is located in the left lobe (28% of cases), epigastric tenderness is noted.

#### Pulmonary abnormalities

- These are present in 20-45% of cases and consist of dullness and rales at the right lung base and nonproductive cough.
- Breath sounds over the right lung base may be diminished.
- Pleural rub may be audible.

Jaundice (<10% of cases) mostly occurs in complicated cases with multiple abscesses or a large abscess compressing the biliary tract.

#### Signs of complications

- Signs of peritoneal irritation, such as rebound tenderness, guarding, and absence of bowel sounds, are present when the abscess ruptures in the peritoneal cavity. Peritonitis occurs in 2-7% of cases.
- Pericardial friction rub can be audible when the abscess extends into the pericardium. This sign is associated with very high mortality.
- Signs of pleural effusion are present when the abscess ruptures in the pleural cavity.

**Causes:** The following are the risk factors associated with amebic liver abscess:

- People who immigrate from endemic areas

- Populations that are institutionalized, especially people with mental retardation
- Persons living communally
- Promiscuous male homosexuals (secondary to sexually acquired amebic colitis)
- Presence of immunosuppression (eg, HIV infection, malnutrition with hypoalbuminemia, alcohol abuse, chronic infections, posttraumatic splenectomy, steroid use)

## **DIAGNOSIS**

Diagnosis of amebiasis is complicated, partly because the disease can affect several areas of the body and can range from exhibiting few, if any, symptoms to being severe, or even life-threatening. In most cases, a physician will consider a diagnosis of amebiasis when a patient has a combination of symptoms, in particular, diarrhea and a possible history of recent exposure to amebiasis through travel, contact with infected persons, or anal intercourse.

It is vital to distinguish between amebiasis and another disease, inflammatory bowel disease (IBD) that produces similar symptoms because, if diagnosed incorrectly, drugs that are given to treat IBD can encourage the growth and spread of the amebiasis organism. Because of the serious consequences of misdiagnosis, potential cases of IBD must be confirmed with multiple stool samples and blood tests, and a procedure involving a visual inspection of the intestinal wall using a thin lighted, tubular instrument (sigmoidoscopy) to rule out amebiasis.

A diagnosis of amebiasis may be confirmed by one or more tests, depending on the location of the disease.

### **Stool examination**

This test involves microscopically examining a stool sample for the presence of cysts and/or trophozoites of *E. histolytica* and not one of the many other intestinal amebas that are often found but that do not cause disease. A series of three stool tests is approximately 90% accurate in confirming a diagnosis of amebic dysentery. Unfortunately, however, the stool test is not useful in diagnosing amebomas or extraintestinal infections.

### **Sigmoidoscopy**

Sigmoidoscopy is a useful diagnostic procedure in which a thin, flexible, lighted instrument, called a sigmoidoscope, is used to visually examine the lower part of the large intestine for amebic ulcers and take tissue or fluid samples from the intestinal lining.

### **Blood tests**

Although tests designed to detect a specific protein produced in response to amebiasis infection (antibody) are capable of detecting only about 10% of cases of mild amebiasis, these tests are extremely useful in confirming 95% of dysentery diagnoses and 98% of liver abscess diagnoses. Blood serum will usually test positive for antibody within a week of symptom onset. Blood testing, however, cannot always distinguish between a current or past infection since the antibodies may be detectable in the blood for as long as 10 years following initial infection.

## **Imaging studies**

A number of sophisticated imaging techniques, such as computed tomography scans (CT), magnetic resonance imaging (MRI), and ultrasound, can be used to determine whether a liver abscess is present. Once located, a physician may then use a fine needle to withdraw a sample of tissue to determine whether the abscess is indeed caused by an amebic infection.

## **PROGNOSIS**

With appropriate therapy, simple amebic colitis is cured rapidly. More invasive forms of amebiasis also respond to therapy, but extensive involvement of the lungs or brain may leave the patient with residual damage. If diagnosis is delayed, patients may die before therapy is started.

Recurrence of amebiasis is common, suggesting that immunity acquired from previous infections is of only limited value in preventing reinfection. However, recurrence of invasive disease is quite rare, perhaps as a consequence of an effective immune response. Indeed, detection of a serologic response to infection is of diagnostic value as it correlates well with invasive disease. The indirect hemagglutination (IHA) test for amebiasis is currently the best indicator of invasive disease. An IHA titer of greater than 1024 usually indicates extraintestinal involvement; a titer of 256 to 512 indicates possible extraintestinal involvement or persistent antibody; and titers less than 128 probably rule out extraintestinal involvement. Enzyme-linked immunosorbent assay (ELISA) tests are available, but limited experience so far prevents their general acceptance over the better-known IHA. Serologic titers do not appear to correspond to protection from reinfection.

Cell-mediated immunity plays a major role in limiting amebic infection and preventing reinfection. Human macrophages activated with concanavalin A or amebic antigen-induced lymphokine will kill virulent amebal trophozoites. Patients with decreased numbers of T cells or cell-mediated immunity are more likely to have invasive amebiasis. Severe amebiasis is also seen in young infants, during pregnancy, and in patients receiving pharmacologic doses of glucosteroids.

## **THERAPY**

Treatment is directed toward relief of symptoms and eradication of *E. histolytica*. The choice of amebicides is based on the location and severity of the infection.

### **Asymptomatic Intestinal Infection**

Drugs active against amebae in the intestinal lumen but ineffective against amebae in tissues are adequate for the treatment of asymptomatic intestinal infections. Diloxanide furoate (Furamide) is effective and is the best tolerated of the luminal amebicides. The recommended dosage is 500 mg, PO, every 8 hours, for 10 days. Flatulence appears to be the only major side effect, with nausea, vomiting, diarrhea, and pruritus occurring less often.

Iodoquinol (Yodoxin) is also effective therapy for intestinal amebiasis and is given in a dose of 650 mg, PO, every 8 hours, for 20 days. Side effects include skin rash, nausea, diarrhea, cramps, and pruritus; with prolonged high dosage, optic neuritis, optic atrophy and peripheral neuropathy may occur. Long-term therapy therefore requires frequent monitoring of visual acuity. Because iodoquinol contains iodine, it should be used with caution in patients with thyroid disease.

Paromomycin (Humatin) may be used in a dosage of 30 mg/kg body wt/day, PO, given in three equal portions, every 8 hours, for 7 days. Although mild side effects of nausea,

vomiting, abdominal cramps, and diarrhea occur occasionally, the major drawback of this medication is its cost.

### **Necrotizing Amebic Colitis, Ameboma**

Moderate and severe amebiasis (necrotizing amebic colitis, or ameboma) should be treated with both a luminal (generally diloxanide furoate) and a systemic amebicide because systemic amebicides alone may not adequately treat intestinal amebic cysts. The systemic amebicide metronidazole is given in a dose of 750 mg, PO, every 8 hours, for 10 days. Mild side effects such as nausea, headache, candidal overgrowth, and a metallic aftertaste are common. Less common side effects include dizziness, vertigo, ataxia, irritability, depression, paresthesias, urticaria, flushing, pruritus, dysuria, cystitis, and dark urine. Disulfiram-like reactions may occur if alcohol is consumed during or within 4 days of metronidazole therapy. Although the carcinogenic potential of metronidazole is of concern, 10- to 14-day courses of therapy are safe. If peroral treatment is not feasible, metronidazole may be given by intravenous injection. A luminal agent such as diloxanide furoate or iodoquinol should be given perorally as soon as feasible following the IV metronidazole.

Dehydroemetine (1.0 to 1.5 mg/kg/day [to a maximum of 90 mg/day], IM, in two equal portions, every 12 hours), and emetine (1 mg/kg/day [to a maximum of 60 mg/day], in two equal portions, every 12 hours) are alkaloid derivatives of ipecac that are highly effective against amebae in tissues. However, both are potentially toxic and may cause hypotension, chest pain, and cardiac arrhythmias. Accordingly, these drugs should be avoided unless all other amebicides have failed or unless the patient is unable to take either peroral medications or intravenous metronidazole.

### **Extraintestinal Amebiasis**

Metronidazole combined with either diloxanide furoate or iodoquinol is generally effective in extraintestinal amebiasis. Relapses occur and should be treated with dehydroemetine (dose as above, for 5 days) followed by chloroquine phosphate base (600 mg/day, PO, for 2 days, followed by 300 mg/day, PO, for 2 to 3 weeks). The potential side effects of chloroquine include pruritus, vomiting, and headache; total doses greater than 100 g may cause permanent retinal damage. A luminal amebicide should be given concomitantly. Percutaneous therapeutic aspiration of amebic liver abscesses is indicated when the lesions are large and are associated with severe localized liver tenderness or marked diaphragmatic elevation. Surgical drainage is rarely necessary, and most amebic liver abscesses heal gradually over a period of 2 to 4 months with appropriate antiamebic therapy. Pleural involvement may require drainage via a chest tube or thoracotomy; surgical exploration of both thorax and abdomen may be necessary.

Although amebiasis generally responds to appropriate chemotherapy, parasitologic relapses do occur and the feces should be checked monthly for several months after therapy. Other household members should also be screened initially for possible asymptomatic infection. In highly endemic areas, asymptomatic carriers are not necessarily treated because the probability of reinfection is high. Food handlers should always be treated, and the most effective means of prevention is proper sanitation. Prophylaxis with amebicides is not recommended.

## **PREVENTION**

Prevention and control of amebiasis are dependent on understanding the cause of endemicity or epidemic outbreaks in a particular community. What is necessary for prevention in one community may be of little value in another. In addition, communitywide programs are of only limited value to the traveler who requires personal protection.

Community resources are best directed at providing safe drinking water through standard water treatment (sedimentation, flocculation, filtration, and chlorination). Proper treatment of sewage is important to prevent contamination of drinking water and to prevent the use of raw sewage to fertilise fields.

Travelers to regions endemic for *E. histolytica* should be aware that contaminated drinking water and food are the most frequent sources of infection. To avoid amebiasis and other enteric pathogens, the traveler should avoid all forms of the local water including ice cubes; raw vegetables and salads; milk, ice cream, and cheese; and food from street vendors. Bottled water should be used for drinking, brushing teeth, and other personal purposes. Carbonated beverages should be drunk without ice; coffee and tea should be taken hot. Only food that has been thoroughly cooked and is hot when brought to the table may be eaten. Fresh fruit that is peeled at time it is eaten is also safe.

## **REMAINING PROBLEMS**

Control of *E. histolytica* remains a major problem in many underdeveloped countries. The means of control are well within the capabilities of all nations but require stable social systems for application. New diagnostic tests that detect amebal antigen in the feces and serum would be useful to differentiate colonization from invasive disease. This would greatly aid physicians faced with patients from areas where *E. histolytica* is endemic.

## **YELLOW FEVER**

Yellow fever is an acute, mosquito-borne viral infection that occurs in epidemic and endemic form in tropical America and Africa, but not in Asia. In its most severe form the disease is characterized by fever, jaundice, hemorrhage, and proteinuria, Mild and abortive forms, with or without jaundice, are common. Yellow fever is classified as one of the viral hemorrhagic fevers; however, the severity of the hepatic injury in this disease distinguishes it from other hemorrhagic fevers.

## **ETIOLOGY**

Yellow fever virus is the prototype of the flavivirus genus (family Flaviridae) . Flaviviruses are small, spherical, enveloped RNA viruses that share antigenic determinants characteristic of the genus. Cross-reactions may thus render the serodiagnosis of yellow fever in endemic zones difficult. Strains of yellow fever virus in tropical America and Africa differ in various laboratory markers but do not clearly differ in the disease they produce in humans. The virus is pathogenic for a variety of cell cultures, infant mice (by intracranial and peripheral inoculation), adult mice inoculated intracranially, and some monkey species (e.g., rhesus, cynomolgus, howler).

## EPIDEMIOLOGY

In tropical America, approximately 50 to 300 cases of yellow fever are recognized annually, but the disease is undoubtedly underreported. The virus circulates principally in the Amazon region, where it is maintained as an enzootic and epizootic infection of monkeys, which is transmitted by *Haemagogus* spp. mosquitoes. Lethal infections occur in some species of monkeys, and deaths herald epizootic spread. If humans come into contact with the jungle transmission cycle and are bitten by *Haemagogus* spp., they may acquire jungle yellow fever as an incidental infection. Thus, yellow fever in humans in tropical America is generally a sporadic disease, although small outbreaks (20 to 50 cases) are not uncommon and dramatic episodes may occur when groups of unvaccinated laborers enter the jungle. Formerly, human-mosquito-human transmission by the peridomestic mosquito *Aedes aegypti* was responsible for large epidemics of *urban yellow fever* in the cities and towns of South America, and as late as 1905 in North America (New Orleans). Eradication of *A. aegypti* from urban areas of most South American countries has precluded urban transmission, and the last such outbreak occurred in Brazil in 1942. However, the reinvasion by *A. aegypti* of areas of Brazil, Bolivia, and Colombia adjacent to the yellow fever enzootic zone and the widespread occurrence of *A. aegypti*-borne dengue in the Caribbean and northern countries of South America are impressive reminders that urban yellow fever could again become epidemic in the Western Hemisphere.

Yellow fever is a more important public health problem in Africa. Epidemics of note in the last 25 years include Ethiopia, 1960- 1962 (100,000 cases); Senegal, 1965 (2000-20,000 cases); Nigeria-Togo-Ghana-Upper Volta-Mali, 1969- 1970 (many thousands of cases); the Gambia, 1978-1979 (8500 cases); and Nigeria and Mali, 1986-1987 (tens of thousands of cases). Endemic infection and sporadic disease, as well as unrecognized epidemics, account for much unreported morbidity. The transmission cycles are complex and continue to be the subject of intensive study. In forested areas, enzootic-epizootic circulation of yellow fever virus occurs between monkeys and a variety of *Aedes* spp. Transmission from monkeys to humans by wild, tree-hole breeding *Aedes* spp. occurs, but epidemics are sustained by a human-mosquito-human cycle involving wild *Aedes* spp. or domestic *A. aegypti*.

Nonimmune persons are equally susceptible, regardless of race, age, or sex. However, the incidence in tropical America is generally higher in adult males because of greater exposure to mosquitoes during wood cutting or agricultural pursuits. Outbreaks occur during the rainy season or early dry season, times of peak vector populations and longevity. The susceptibility of a given population of humans is closely related to the level of immunity to yellow fever (naturally acquired or vaccine-induced) and possibly also influenced by heterologous immunity engendered by closely related, non-yellow fever flaviviruses.

## PATHOGENESIS AND PATHOLOGY

Early in the infection with yellow fever virus, viral replication, as manifested by cytopathology, is limited to the Kupffer's cells. Spread to hepatocytes follows. The resulting injury and death of infected liver cells leads to hepatic failure, with the accumulation and appearance in the blood of metabolites normally processed by the liver and substances normally confined inside hepatocytes.

In all severe cases, some degree of renal failure is present. The pathogenesis is not clear but may be related to primary injury from invasion of kidney cells by yellow fever virus, or renal failure secondary to hepatic failure. The latter mechanism is favored by the finding of a decrease in renal perfusion preceding the development of acute tubular necrosis in monkeys infected experimentally with yellow fever virus.

Circulatory shock, acidosis, and hyperkalemia appear to be late events in fatal yellow fever. Hemorrhage may exacerbate the hypotension. Disseminated intravascular clotting may occur, but hemorrhage is usually caused by decreased synthesis of vitamin K-dependent clotting factors by the liver.

The histopathologic changes in the liver characteristic of yellow fever include coagulative necrosis of hepatocytes in the midzone of the liver lobule with sparing of cells bordering on the central vein; eosinophilic degeneration of liver cells (Councilman bodies); intranuclear eosinophilic granular inclusions (Torres bodies); multivacuolar and microvacuolar fatty changes sparing of the reticulin framework; and absence of inflammation. However, this classic array of findings is not always present. The histopathology is frequently atypical or difficult to interpret, especially when death occurs after the 10th day of illness. Other conditions, for example, Lassa, Marburg-Ebola virus infections, and the usual viral hepatitis must be differentiated from atypical cases of yellow fever.

Changes in other organs include acute tubular necrosis and fatty vacuolization of the kidneys, depletion and necrosis of the lymphocytic elements in the spleen and lymph nodes, cloudy swelling and degeneration of myocardial fibers, and edema and petechial hemorrhages in the brain.

## MANIFESTATIONS

After an incubation period of 3 to 6 days, clinically evident yellow fever varies from very mild to fatal disease. Mild cases are frequent, occurring in 80% to 90% of those infected. The manifestations include fever, headache, malaise, and lassitude, which persist for 2 to 4 days. Since the illness is clinically nonspecific, the diagnosis of yellow fever will be suspected only in the setting of an epidemic and can be confirmed only by laboratory tests.

The classic syndromes of yellow fever occur in 10% to 20% of persons infected. The onset is abrupt, with fever to 40°C (104°F), chills or chilliness, headache, and myalgias. Nausea, vomiting, and minor gingival bleeding or epistaxis may occur. The patient appears to be in acute distress, with flushing of the face and a tongue red at the tip and edges. The pulse is slow in relation to the fever (Faget's sign). This syndrome may last several days and is named the *period of infection* because yellow fever virus is present in the blood. The patient may then have a brief (several hours to 24 hours) *period of remission* of fever and symptoms. This is followed by a *period of intoxication*, during which disease reappears and progresses. Fever increases, with frequent vomiting, epigastric pain, prostration, increasing proteinuria, oliguria, jaundice, and hemorrhage, especially hematemesis. The case-fatality rate in severe cases approaches 50%. Deaths generally occur 7 to 10 days after onset of illness. Hypothermia, hypotension, delirium or stupor, coma, and intractable hiccup are terminal events.

In patients surviving severe yellow fever, convalescence may be prolonged and is associated with asthenia lasting several weeks. Late deaths, attributed to heart failure or arrhythmias, have been recorded.

During convalescence, patients may die from acute tubular necrosis and complicating bacterial sepsis. Secondary bacterial pneumonias are frequent.

## DIAGNOSIS

The diagnosis of yellow fever should be considered in nonvaccinated persons with a febrile illness who have a history of travel within endemic areas. Early in the illness, the number of leukocytes and blood platelets is normal or depressed. In severe cases, there is prolongation of the clotting, prothrombin and partial thromboplastin times. The serum

transaminase concentrations are markedly elevated in cases with jaundice but may or may not be abnormal in mild, anicteric infections. The total and conjugated serum bilirubin concentrations rise simultaneously and may reach 15 mg to 20 mg/dl. The blood glucose may fall preterminally. The urine contains a small amount of protein during the period of infection; the concentration rises abruptly to levels of 3 g to 5 g/liter (occasionally higher) during the period of intoxication. Nonspecific ST-T wave electrocardiographic changes may be present.

Specific diagnosis is achieved by isolating virus from blood taken during the period of infection or by demonstrating circulating viral antigen by immunoassay. A presumptive serologic diagnosis may be achieved during the first week by detecting IgM antibody by enzyme immunoassay. A confirmatory serologic diagnosis requires demonstration of a rise in titer of antibody, comparing serum obtained as early after the onset as possible with a specimen taken 10 to 14 days later. The hemagglutination-inhibition, indirect fluorescent antibody, complement fixation, enzyme-linked immunosorbent assay, and neutralization tests are useful. Of these, the IgM immunoassay and neutralization tests are the most specific, a matter of some importance as cross-reactions with heterologous flaviviruses may complicate serologic diagnosis. Liver biopsy is not an acceptable means of diagnosis because of the bleeding diathesis. Postmortem examination of the liver may provide a specific diagnosis; tissues other than liver (especially spleen and lymph nodes) should also be subjected to study. The virus may occasionally be isolated from the liver. Other diseases that may be confused with yellow fever include viral hepatitis, falciparum malaria, leptospirosis, typhoid fever, Rift Valley Fever, Congo-Crimean hemorrhagic fever, rickettsial infections, and surgical and toxic conditions. Argentine and Bolivian hemorrhagic fever, dengue, Lassa, Marburg, and Ebola virus diseases must also be considered; jaundice is generally not a feature of these infections. Mild yellow fever cannot be distinguished clinically from a large number of febrile diseases.

## PROGNOSIS

The case-fatality rate in all patients with clinical illness is probably 2% to 5%; however, in severe cases, it may be as high as 50%. A poor prognosis is augured by the appearance of a period of intoxication, rising proteinuria and bilirubinemia, progressive oliguria, marked prolongation of the prothrombin time, and severe hemorrhage.

## THERAPY

There is no specific treatment for yellow fever, and the intensive application of nonspecific therapies is largely of unproven value because patients with severe yellow fever are usually cared for in relatively primitive facilities. Yet, it is known that complete hepatic regeneration occurs in patients who survive the acute disease, providing a rationale for vigorous supportive efforts. Thus, nonaspirin analgesics, anti-emetics, and water and electrolytes should be administered during the acute infection. Nasogastric suction should be used to prevent gastric distention, and cimetidine should be given to reduce the risk of gastric hemorrhage. During the period of intoxication, intensive care similar to that provided for other forms of acute hepatic and acute renal failure is necessary. Monitoring renal function—for example, by measuring the excreted fraction of sodium, and efforts to maintain fluid balance and combat hypotension may be helpful in preventing progression of uremia. Some patients may require peritoneal dialysis or hemodialysis. In cases of *documented* disseminated intravascular clotting, the use of heparin should be considered. Secondary bacterial infections should be treated with appropriate antimicrobics.

## PREVENTION

The acutely ill patient should be placed under a bed net to prevent contact with mosquito vectors. Care should be taken to prevent accidental infection of others by contaminated needles.

Yellow fever 17D vaccine (a live attenuated strain of yellow fever virus) is a safe and highly effective means of immunoprophylaxis. Immunity is demonstrable within 10 days after vaccination and provides protection for at least 30 years (probably for a lifetime). The vaccine rarely causes mild systemic reactions. Because the vaccine strain is propagated in chick embryos, it should be used with caution in persons with a history of allergy to hens' eggs. Although no harmful effects on the developing fetus have been documented, the vaccine should not be used during pregnancy unless there is a high risk of natural yellow fever infection.

Prevention of outbreaks mediated by *A. aegypti* depends primarily on elimination of sites suitable for the peridomestic breeding of this mosquito. Infections acquired from wild mosquito vectors can be prevented by vaccinating the human population at risk.

## REMAINING PROBLEMS

More information is needed about the ecology of yellow fever to define the factors responsible for the recrudescence of epidemics and the mechanisms that maintain enzootics. The possibility of large *A. aegypti*-borne outbreaks of yellow fever in the Caribbean, southern United States, or even Asia remains a threat.

The pathogenesis and pathophysiology of yellow fever (and other viral hemorrhagic fevers) remain ill-defined. Clarification may lead to improved, specific, and supportive therapies. Presently available intensive care capabilities should be evaluated in experimental yellow fever (preferably in nonhuman primates) and in clinical studies.

Improved methods for rapid and early diagnosis are required. Current vaccine production is inadequate to meet potential pandemic situations of commitments to mass vaccination campaigns in endemic areas such as West Africa. Modernisation of vaccine production by the use of cell cultures for propagation of the 17D virus strain should be investigated as an alternative to the chick embryo.

## DENGUE

Dengue fever is a benign, acute febrile syndrome caused by several arthropod-borne viruses; it is generally confined to tropical areas and characterized by biphasic fever, myalgia or arthralgia, exanthem, leukopenia, and lymphadenopathy. The term "dengue" is a Spanish homonym for the African "*ki denga pepo*" introduced into the English literature during an 1827- 1828 Caribbean outbreak probably caused by chikungunya virus. Dengue viruses also cause an acute vascular permeability syndrome accompanied by abnormalities of hemostasis (dengue hemorrhagic fever) and, frequently, hypotension (dengue shock syndrome). In the modern era, dengue hemorrhagic fevendengue shock syndrome (DHF/DSS) has most often involved Asian children. DHF/DSS is thought to have an immunologic basis.

## ETIOLOGY

Dengue viruses are enveloped RNA viruses classified in the family Flaviviridae. At least four clearly defined types exist; genetic, antigenic, or biologic variants are found in the American and Asian tropics. Cross comparisons by the plaque reduction neutralization test show the dengue viruses to be an antigenic subgroup within the flaviviruses. All flaviviruses share group antigens best demonstrated by the hemagglutination-inhibition test. Each of the dengue viruses causes closely related clinical illnesses. After a short period of cross-protection, a person is fully susceptible to infection with a different type. This heterotypic infection is accompanied by a secondary type antibody response. Homotypic immunity is lifelong. Nondengue virus causes of the dengue fever syndrome are discussed under Diagnosis.

## EPIDEMIOLOGY

Dengue viruses are widely distributed in tropical countries girdling the globe. In 1980, dengue virus was transmitted within the continental United States for the first time in nearly 40 years. This event, plus recent epidemic activity in South China, Taiwan, and northern Australia calls attention to the fact that contemporary demographic and ecologic conditions favor episodic extension of dengue viruses into subtropical areas. Year-round transmission occurs between 25° north and south.

*Aedes aegypti*, a daytime biting mosquito, is the principal vector in dengue fever. In most tropical areas, *A. aegypti* is highly domesticated, breeding in water stored for drinking or bathing or in any container that collects fresh water. The eggs resist desiccation and hatch following immersion. In some outbreaks, *Aedes albopictus*, *Aedes polynesiensis*, and *Aedes scutellaris* have been implicated as vectors. Following the ingestion of viremic blood, dengue viruses replicate in the mosquito's gut and eventually infect the salivary glands. This process normally requires 8 to 11 days and constitutes the extrinsic incubation period. *Aedes aegypti* preferentially feeds on human beings. Mosquitoes are infectious for a lifetime. Because female mosquitoes take repeated blood meals, long-lived females have great potency as vectors. Dengue virus may also be transmitted mechanically by reflux of viremic blood through the mosquito's proboscis during interrupted feeding.

When *A. aegypti* are abundant, the epidemiology of dengue resembles that of respiratory viruses. Transmission is increased in densely populated areas. The virus moves primarily with viremic hosts, because *A. aegypti* has a limited flight range.

The existence of a jungle dengue cycle has been documented in Malaysia, involving canopy-feeding monkeys and *Aedes niveus*, a species that feeds on both monkeys and humans. A similar sylvan cycle appears to exist in West Africa, where laboratory studies suggest that mosquitoes may serve as an auxiliary reservoir by sexual and transovarial transmission of virus. The full geographic extent of the zoonotic reservoir is unknown. At present, *A. aegypti* and susceptible humans are so numerous that the impact of the jungle cycle is hardly discernible.

An outbreak in Cuba in 1981 resulted in 116,000 hospitalizations (more than 1% of the total population) in a little over 3 months. Deaths occurred in all age groups, but classic shock syndrome was predominantly a pediatric problem. Although infected equally, blacks had DHF/DSS less commonly than did whites. This outbreak accompanied the introduction of dengue 2 into a population immunized to dengue 1 as the result of a relatively silent dengue 1 epidemic beginning in 1977.

In DHF-endemic countries, all four types of dengue virus characteristically circulate in urban areas where there are dense populations of *A. aegypti*. Sequential infections are

common. Clinical and prospective epidemiologic studies have shown that DHF/DSS occurs during second dengue infections in children who are 1 year of age or older and in infants less than 1 year born to dengue-immune mothers. Although third and fourth sequential infections are theoretically possible, age-specific hospitalization data suggest that persons are at risk of DHF/DSS only during their second infection. Repeated attacks of life-threatening shock syndrome in the same person have not been reported.

There is a strong association in the Asian tropics between DHF/DSS and the presence of heterotypic antibodies before infection. Except for the 1981 Cuban outbreak, this relationship does not hold in the Indian, African, and American tropics where populations also have been exposed to several serotypes. In general, annual infection rates and, therefore, the frequency of sequential infections are lower in these latter areas than in South East Asia. Other possible explanations for this heterogeneous distribution are considered later in this chapter.

## **MANIFESTATIONS**

### **Dengue Fever**

Biphasic fever and rash are the most characteristic features of the dengue fever syndrome. Manifestations vary with age and from patient to patient. In infants and young children, the disease may be undifferentiated or characterized by a 1 - to 5 -day fever, pharyngeal inflammation, rhinitis, and mild cough.

Although the mean incubation period, duration of illness, and spectrum of clinical findings may characterize infection with each type of dengue, this is not fully established. In outbreaks of dengue, a majority of infected adults have most of the findings summarized below.

After an incubation period of 2 to 7 days, there is an abrupt onset of fever that rapidly rises to 39.5°C to 41.4°C usually accompanied by frontal or retro-orbital headache. Occasionally, back pain precedes the fever. A transient, macular, generalized rash that blanches under pressure may be seen during the first 24 to 48 hours of fever. The pulse rate may be slow in proportion to the degree of fever. Myalgia or bone pain occurs soon after onset and increases in severity. During the second to the sixth day of fever, nausea and vomiting are apt to occur, and during this phase general lymphadenopathy, cutaneous hyperesthesia, taste aberrations, and pronounced anorexia may develop.

Coincident with or 1 or 2 days after defervescence, a morbilliform, maculopapular rash that spares the palms and soles appears. The rash then disappears in 1 to 5 days. In some cases there is edema of the palms and soles. Desquamation may occur. About the time of appearance of this second rash, the body temperature may become slightly elevated to establish a biphasic temperature curve.

Epistaxis, petechiae, and purpuric lesions, though uncommon, may occur at any stage of the disease. Swallowed blood from epistaxis may be passed by rectum or vomited and may be interpreted as bleeding of gastrointestinal origin. Gastrointestinal bleeding, menorrhagia, and bleeding from other organs have been observed in adults in some outbreaks of dengue fever, apparently without concurrent thrombocytopenia or hypovolemia. The mechanisms of hemostatic abnormalities in these cases are unknown.

Some cases develop much milder symptoms, which can, when no rash is present, be misdiagnosed as a flu or other viral infection. Generally, younger children have a milder illness than older children and adults. The classic dengue fever lasts about six to seven days, with a smaller peak of fever at the trailing end of the fever. Dengue fever should not be confused with Dengue hemorrhagic fever (DHF), which is a separate disease and frequently fatal.

### **Dengue Hemorrhagic Fever (DHF)/Dengue Shock Syndrome (DSS)**

The incubation period of DHF is unknown but is presumed to be that of dengue fever. In children, the progression of the illness is characteristic. A relatively mild first phase with abrupt onset of fever, malaise, vomiting, headache, anorexia, and cough is followed after 2 to 5 days by rapid deterioration and physical collapse. The median day of admission to hospital after onset of fever is day 4. In this second phase, the patient usually manifests cold, clammy extremities, warm trunk, flushed face, diaphoresis, restlessness, irritability, and usually midepigastic pain. Frequently, there are scattered petechiae on the forehead and extremities, spontaneous ecchymoses may appear, and easy bruisability and bleeding at sites of venipuncture are common. The tourniquet test is positive. There may be circumoral and peripheral cyanosis. Respirations are rapid and often labored. The pulse is weak, rapid, and thready, and the heart sounds are faint. The pulse pressure is frequently narrow (120 mm Hg); the systolic and diastolic pressures may be low or unobtainable. The liver may become palpable 2 to 3 fingerbreadths below the costal margin and is usually firm and nontender.

Approximately 10% of children manifest ecchymoses or gastrointestinal bleeding. In adults, it appears that the severity of hemorrhagic phenomena is disproportionate to the degree of hypotension. After a 24- or 36-hour period of crisis, convalescence is fairly rapid. The temperature may return to normal before or during the stage of shock.

By definition, a patient with DHF must exhibit thrombocytopenia ( $<100,000/\mu\text{l}$ ) and hemoconcentration (hematocrit  $>120\%$  of the recovery value); the addition of a narrow pulse pressure or hypotension completes the requirements for the dengue shock syndrome. The number and degree of laboratory abnormalities increase with the severity of disease. Elevations in transaminases, metabolic acidosis, hypovolemia and hypoproteinemia are common. Roentgenograms of the chest may reveal bronchopneumonia and pleural effusion. Hematologic abnormalities include hypofibrinogenemia, increased fibrin split products, prolonged bleeding and silicone clotting times, moderate prolongation of prothrombin time with deficiencies in Factors V, VII, IX, and X. In children, the degree of complement depletion and the concentrations of circulating fibrin split products relate directly to the severity of shock. In adults, disseminated intravascular coagulation may be relatively severe. Hematuria and proteinuria are rarely seen. Acute central nervous system (CNS) findings are of uncertain etiology but may be the result of cerebral edema. Occasionally, intracranial bleeding may produce severe and more permanent damage of the CNS.

DHF and DSS are potentially deadly but patients with early diagnosis and appropriate therapy can recover. DHF requires continuous monitoring of vital signs and urine output. DSS is a medical emergency that requires intensive care unit hospitalisation

The increase in dengue mortality is considered to be a reflection of the increase in the proportion of DF patients who develop DHF/DSS.

### **DIAGNOSIS**

The clinical diagnosis of the dengue fever syndrome derives from a knowledge of the geographic distribution and ecology of viral causes of this syndrome and possible exposure of the patient at an appropriate interval prior to onset of disease.

The differential diagnosis of fever and myalgia includes many other viral and bacterial diseases and the early stages of malaria, scrub typhus, hepatitis and leptospirosis. Abortive forms of the latter diseases may never evolve beyond a denguelike stage. Three common

arbovirus exanthems are denguelike: chikungunya and O'nyong nyong fevers (alphaviruses) and West Nile fever (flavivirus). Three others are denguelike but without rash: Colorado tick fever, sandfly fever, and the mild form of Rift Valley fever. Each of these is an acute febrile disease with an incubation period of a few days. Because of the variation in clinical findings and the multiplicity of possible causative agents, the descriptive term *denguelike disease* should be used until a specific etiologic diagnosis is provided by the laboratory.

In areas endemic for dengue viruses, DHF/DSS should be suspected in persons exhibiting hemoconcentration with thrombocytopenia. Shock, hemorrhagic manifestations (including a positive tourniquet test), and hepatic enlargement are common accompanying findings. Since many rickettsial diseases, meningococemia, and other severe illnesses caused by a variety of agents may produce a similar clinical picture, the diagnosis should be made only when epidemiologic or serologic evidence is consistent with dengue. Hemorrhagic manifestations have been described in other diseases of viral origin these include the arenavirus hemorrhagic fevers of Argentina, Bolivia, and West Africa, Ebola and Marburg disease, the tick-borne hemorrhagic fevers of India and the Soviet Union, and hemorrhagic fever with renal syndrome which occurs across northern Eurasia from Scandinavia to Korea.

Etiologic diagnosis may be based on detection of specific IgM in serum and by conventional tests of properly collected acute and convalescent serum samples, or by isolation of the virus. Acute-phase serum samples for virus isolation or serologic study should be obtained during the febrile period, preferably before the fourth day after onset of illness. Serum for IgM-capture tests may be collected up to several weeks after illness. A second specimen of serum should be taken 2 weeks or more after onset. The acute-phase serum or plasma may be frozen, optimally at  $-65^{\circ}\text{C}$  or colder, to preserve the specimen for virus isolation. In conventional tests, serologic diagnosis depends on demonstrating a fourfold or greater increase in antibody titer. Anti-dengue IgM is produced transiently during both primary and secondary infections; detection of it in any single serum sample indicates an active or recent infection. Anti-dengue IgG is also produced in primary and secondary dengue infections but the quantity of IgG produced is much greater in secondary than in primary infections. Solid-phase antibody-capture ELISA provides a sensitive method of quantitating IgM and IgG antibodies. Following primary infections, relatively type-specific neutralizing antibodies are formed. Usually, it is not possible to identify the infecting virus following secondary dengue infections using serologic methods. Sequential infections with dengue and non-dengue flavivirus, or *vice versa*, result in the production of type-specific IgM directed against the second infecting virus.

Differentiation of a primary from a secondary antibody response may be accomplished using the hemagglutination-inhibition (HI) test. With standardized test procedures, in a primary response (1) the HI antibody titer is generally less than 1:20 in serum obtained on or before the fourth day after onset of illness; or (2) there is antibody in the acute-phase specimen, with a fourfold or greater rise in titer in the convalescent serum to a level that does not exceed 1:1280. In a secondary response (1) HI antibody is detected in a specimen of serum collected before the fifth day after onset, with a fourfold or greater rise in antibody titer to at least 1:2560; or (2) no HI antibody is detected in serum collected prior to the fifth day after onset, with an antibody rise to a titer of at least 1:2560; or (3) there are high, fixed HI antibodies at a titer of 1:1280 or greater in paired sera.

Acute-phase serum, mosquito suspensions, or other materials thought to contain dengue virus may be inoculated into suckling mice, several tissue cultures, or mosquitoes (intrathoracic injection) of the *Toxorhynchites* or *Stegomyia* genera. The presence of virus in mosquitoes may be detected by fluorescent antibody, complement fixation, or inoculation of mosquito suspensions in tissue cultures.

## **PROGNOSIS**

Prolonged asthenia, mental depression, bradycardia, and ventricular extrasystoles are relatively common after dengue virus-caused dengue fever. Chikungunya infections may result in residual polyarthralgia and arthritis. There is evidence that the prognosis in dengue is adversely affected in persons who have experienced prior dengue infection or passively acquired dengue antibody. The relation of other flavivirus infections to DHF/DSS is not known.

Death occurs in 5% to 40% of children with shock. Adults rarely have shock syndrome, but when it occurs, the prognosis is poor. From the Cuban experience, fatalities in secondary dengue 2 infections are five times more common in those under the age of 15 years than in older persons. Survival is directly related to early hospitalization and the intensity of physiologic management. Infrequently there is residual brain damage either from prolonged shock or from intracranial hemorrhage.

## **THERAPY Dengue Fever**

Treatment of patients with dengue fever is supportive. Bed rest is advised during the febrile period. It may be advisable to avoid salicylates because they may cause bleeding or acidosis. Antipyretics or cold sponging should be used to keep the body temperature below 40°C ( 104°F). Analgesics or mild sedation may be required to control pain. Fluid and electrolyte replacement therapy is required when there are deficits due to sweating, fasting, thirsting, vomiting, or diarrhea.

## **Dengue Hemorrhagic Fever/Dengue Shock Syndrome**

Critical to management of DHF/DSS is immediate assessment of hemoconcentration and electrolyte imbalances. Close monitoring is essential for at least 48 hours, because shock may occur or recur precipitously. Patients who have labored breathing or are cyanotic should be given oxygen. Rapid intravenous replacement of fluids and electrolytes is frequently sufficient to sustain patients until spontaneous recovery occurs. When elevation of the hematocrit persists after vigorous fluid replacement, plasma or colloid preparations are indicated. Care must be taken to avoid overhydration, which may contribute to cardiac failure. Transfusion of fresh blood may be required, but should not be given during hemoconcentration.

Paraldehyde, chloral hydrate, or a benzodiazapine derivative may be required for persons who are markedly agitated. Heparin may be used for those with intractable bleeding, but only if there is objective evidence of disseminated intravascular coagulation. Neither glucosteroids nor the administration of immune serum have any effect on the duration of disease or prognosis.

## **PREVENTION**

No vaccines for dengue viruses or other viral causes of denguelike syndromes are commercially available. Control of *A. aegypti* or avoiding mosquito bites are the only available means of protection. Individual measures include destruction of sites suitable for the breeding of *A. aegypti*. Disposal of all unused objects that may collect water (e.g., old tires, empty tins and bottles, broken jars) and routinely changing the water in flower vases once a week is important. Water storage jars should be emptied by turning upside down once a week. Coconut shells and husks should be buried or burned, tree holes filled with sand or cement, leaf axils punctured and bamboo fences altered so as to prevent accumulation of water. Stored

water should be protected with a tight-fitting lid or a thin layer of oil to prevent egg laying or hatching. Ultra-low-volume spray equipment mounted on truck or airplane effectively dispenses malathion for rapid intervention by killing adult mosquitoes during an epidemic.

## **EPIDEMIC HEMORRHAGIC FEVERS**

The term hemorrhagic fever was first used in the 1930s by Soviet and Japanese scientists to describe an acute febrile disease that occurred in eastern Siberia and northern Manchuria. Subsequently, the same syndrome was reported from Korea, Bulgaria, Hungary, China, European Russia, and northern Scandinavia under several labels, including epidemic hemorrhagic fever, Korean hemorrhagic fever, hemorrhagic nephrosonephritis, nephropathia epidemica, and hemorrhagic fever with renal syndrome (HFRS). Since 1940, nine other nosologic hemorrhagic fevers have been recognized: Omsk hemorrhagic fever (OHF), Kyasaanur Forest disease (KFD), dengue hemorrhagic fever (DHF), Crimean hemorrhagic fever (CHF), Rift Valley fever (RVF), Argentine hemorrhagic fever (AHF), Bolivian hemorrhagic fever (BHF), Lassa fever (LF), and Marburg and Ebola diseases-collectively designated African hemorrhagic fevers (AFHF). All of these diseases are caused by RNA-containing viruses, and all are loosely united by the fact that hemorrhage and shock are their most conspicuous clinical characteristics. This is not to say that other acute viral diseases do not produce hemorrhage-yellow fever is indubitably prototypic of hemorrhagic viral disease. However, the pattern of acute fever with a hemorrhagic diathesis without other striking stigmata provides a convenient basis for grouping a variety of diseases into a single, broad clinical syndrome.

### **ETIOLOGY**

The viruses that cause hemorrhagic fevers are diverse. Three diseases, OHF, KFD, and DHF, are caused by arthropod-borne flaviviruses; the first two are members of an antigenic complex of agents transmitted by ticks, while DHF belongs to a mosquito-borne complex within the genus *Flavivirus*. Three other diseases are caused by viruses belonging to the large family *Bunyaviridae*. The virus of RVF belongs to the genus *Phlebovirus*, that of CHF is a *Nairovirus*, and the agent of HFRS, the most recently isolated hemorrhagic fever virus, is the prototype of a new genus, *Hantavirus*.

Junin, Machupo, and Lassa viruses are arena-viruses, morphologically indistinguishable from lymphocytic choriomeningitis virus of mice (LCM). The first two are causative agents of AHF and BHF, respectively, and are closely related antigenically. Lassa virus, which causes LF, shares antigens with LCM.

Marburg and Ebola viruses are morphologically similar but antigenically distinct viruses that share certain properties with rhabdoviruses, the family to which rabies virus belongs. The name *filoviridae* has been proposed for these unique agents.

The viruses that cause epidemic hemorrhagic fever represent several taxonomic families and genera, and they differ widely in size, shape, biochemical structure, and immunologic properties. Yet, two fundamental characteristics appear to be common: all have lipid-containing outer membranes, and all have genes composed of RNA.

Infections are mainly transmitted from nonhuman animals to humans. Thus, individual diseases are strongly focal in occurrence, and their geographic distribution is coincident with that of various complex biologic systems that involve wild or domestic vertebrates and arthropods. Each disease has a definite seasonal pattern, although LF has been demonstrated to be an endemic disease with a very modest seasonal peak. CHF, OHF, and KFD are tick-

borne; DHF is mosquito-borne; HFRS, AHF, BHF, and LF are principally transmitted to humans by contact with infectious urine or feces from chronically infected rodents. Although the epidemiology and ecology and AFHF are still unknown, it appears that the principal mode of transmission is contact with blood or excretions from patients with the disease.

All but DHF, LF, AFHF, and to a lesser extent BHF are diseases in which occupational exposure to critical vertebrate or arthropod vectors largely determines attack rates and age and sex patterns of disease. In contrast, DHF is urban and is concentrated in cities where certain *Aedes* spp are numerous and where infection with more than one type of dengue virus is highly endemic; moreover, DHF occurs almost exclusively in children (no sex difference). The mild form of HFRS also has an urban distribution and is caused by a hantavirus carried by *Rattus norvegicus*.

## MANIFESTATIONS

The outstanding manifestations of epidemic hemorrhagic fevers are depicted in. Fever is high and unremitting in most syndromes and is frequently biphasic in OHF and KFD. The patients appear to be very sick, exhibiting suffusion of the skin about the face and upper trunk and conjunctival injection. Complaints of severe myalgias and localized abdominal pain have sometimes led to ill-advised laparotomy. Acute hepatitis, generally nonicteric, is characteristic of CHF, RVF, LF, and AFHF. In addition to melena and hematemesis, bleeding may occur from the nose, uterus, lungs, and gingivae in all syndromes. Petechiae, although sparse, are usually found on the upper chest, shoulders, neck and palate. Major ecchymotic lesions have been reported in CHF.

Shock is of minor importance in OHF and KFD but is a major feature in all other hemorrhagic fevers. Typically, this process begins with a progressive fall in blood pressure 4 to 10 days after the onset of fever. At this stage, the process is generally reversible by careful use of plasma expanders and fluids. If unrecognized, however, it progresses to shock with tachycardia, pallor, and cold, moist skin. For 1 to 2 days of crisis, life hangs in the balance; protein and fluid therapy at this stage frequently produces irreversible pulmonary edema and death.

Encephalitic manifestations are at least as prominent as hemorrhage in OHF, KFD, and RVF, and a patchy bronchopneumonia is part of the primary disease in OHF. Encephalopathy in AHF and BHF produces intention tremor of the tongue and the muscles of the pharynx and larynx. There may be progression to intention tremors of the extremities and general convulsions. In these arenaviral infections, the cerebrospinal fluid contains neither virus nor cells, and the concentration of protein is normal.

Distinguishing features of Lassa fever include a stormy, febrile course 2 to 3 weeks in duration; an exudative pharyngitis; clinical and pathologic evidence of myocarditis and hepatitis; and the frequent (5%- 10%) occurrence of central deafness, either unilateral or bilateral.

## DIAGNOSIS

Clinically, however, many cases of hemorrhagic fever, particularly those in which hemorrhage is initially minimal or absent, are difficult to differentiate from such infections as malaria, yellow fever, murine typhus, leptospirosis, typhoid fever and a variety of undifferentiated arbovirus diseases. Because the non-viral infections on this list are specifically treatable, they should be rigorously excluded by appropriate laboratory tests in all instances where the clinical and epidemiologic data are compatible with hemorrhagic fever.

Specific diagnosis may be made by measurement of antibodies or isolation of viruses. In virtually all cases of HFRS and in about two-thirds of the cases of LF, patients have virus-specific IgM antibodies in their blood at the time of admission to hospital. In the other diseases, bloodborne virus may be isolated and identified within 1 to 7 days after inoculation of baby mice or hamsters or appropriate cultured cells. Detection of increasing titers of antibodies by comparing titers in acute and convalescent specimens of serum also serves to confirm the diagnosis, but is not helpful in guiding therapy.

The prognosis varies widely. Mortality figures are not comparably reliable for all hemorrhagic fevers, but there is no doubt that Ebola virus disease is the most lethal of the viral infections of humans, other than rabies and, probably, infection with human immunodeficiency virus. Shock, secondary bacterial infection, hepatitis, and preexistent chronic diseases are most commonly cited as causes of death in fatal infections. In general, patients who survive the acute manifestations recover completely and are immune thereafter; antibodies persist for many years and second attacks have not been documented.

### **THERAPY**

Specific therapy is now available for two arenaviral hemorrhagic fevers, namely AHF and LF. When administered prior to the eighth day of clinical disease, 250ml convalescent human plasma reduced mortality in AHF from 16% to 1%. This effect was accompanied by neutralization of Junin virus in the blood of treated patients. In contrast, plasma from patients convalescent after LF disease contains little virus-neutralizing activity and has no therapeutic benefit. Treatment of severely ill patients with the antiviral drug ribavirin ( 15 mg/kg body wt, IV, 6-hourly, for 4 days; then 7.5 mg/kg body wt, IV, q-hourly, for 6 days) reduced the mortality from 55% to 5%. Ribavirin is under evaluation in the treatment of HFRS. In nonhuman animals, ribavirin appears to be effective against RVF as well.

### **PREVENTION**

Although work has advanced on DHF, AHF, and LF, there are as yet no effective vaccines for any viral hemorrhagic fever. BHF was effectively prevented by a control program directed at the peridomestic rodent reservoir-vector *Calomys callosus*, and such programs might be applied to HFRS and LF in limited situations. The prevention of DHF consists of measures long used in the control of yellow fever because the principal mosquito vector is *Aedes aegypti*. To date, however, affected cities have not mobilized the necessary resources. Soviet workers have reported success in the control of OHF by using large-scale aerial application of DDT to reduce tick populations. Individual protection against arthropod-borne hemorrhagic fevers is offered by insect repellents applied to the skin or impregnated into outdoor clothing.

### **REMAINING PROBLEMS**

DHF, HFRS, and LF occur with sufficient frequency and regularity to warrant continued efforts toward development of effective vaccines. Work is now focused on molecular approaches to this goal for all three goals.

The therapeutic breakthrough with ribavirin in LF lends encouragement to further screening of antiviral compounds for other hemorrhagic fevers. Considering the rural setting and the epidemic pattern of many of the hemorrhagic fevers, specific therapy offers the best medium-term hope for reducing morbidity and mortality, and, perhaps, for preventing clinical disease.

The pathologic mechanism(s) that produce capillary damage and shock are imperfectly understood. Studies of LF in nonhuman primates suggest that endothelial biochemical function is somehow impaired. Elucidation of this phenomenon might rationalize improved supportive therapy for many of the hemorrhagic fevers.

## CHIKUNGUNYA VIRUS INFECTION

### Epidemiology

Geographical distribution of the virus is probably restricted. The virus spreads in East Asia, or Africa. The virus is known to occur in subtropical regions, or tropical regions; viral host lives under aerobic conditions; viral host lives in the atmosphere. The virus occurs in Angola, or Benin, or Burkina Faso, or Burundi, or Cambodia (Kampuchea), or Cameroon, or the Central African Republic, or Chad, or the Congo, or Cote d'Ivoire, or East Timor, or Gabon, or Gambia, or Ghana, or Guinea Bissau, or Lesotho, or Liberia, or Malaysia, or Mozambique, or Namibia, or Niger, or Nigeria, or Rwanda, or Senegal, or Sierra Leone, or Somalia, or South Africa, or Tanzania, or Thailand, or Togo, or Uganda, or Viet Nam, or Zambia, or Zimbabwe.

Chikungunya is a relatively rare form of viral fever caused by an alphavirus that is spread by mosquito bites from the *Aedes aegyptii* mosquito ,though recent research by the Pasteur Institute in Paris claims the virus has suffered a mutation that enables it to be transmitted by *Aedes albopictus* (Tiger mosquito). This was the cause of the plague in the Indian Ocean and a threat to the Mediterranean coast at present, requiring urgent meetings of health officials in France, Italy, and Spain.

The name is derived from the Makonde word meaning "that which bends up" in reference to the stooped posture developed as a result of the arthritic symptoms of the disease. The disease was first described by Marion Robinson and W.H.R. Lumsden in 1955, following an outbreak on the Makonde Plateau, along the border between Tanganyika and Mozambique, in 1952. Chikungunya is closely related to O'nyong'nyong virus.

### *Chikungunya in Asia (1960-1982)*

Between 1960 and 1982, outbreaks of Chikungunya fever were reported from Africa and Asia. In Asia, virus strains have been isolated in Bangkok in 1960s; various parts of India including Vellore, Calcutta and Maharashtra in 1964; in Sri Lanka in 1969; Vietnam in 1975; Myanmar in 1975 and Indonesia in 1982.

### *Recent occurrences of chikungunya fever*

After an interval of more than 20 years, chikungunya fever has been reported from several countries including India, and various Indian Ocean islands including Comoros, Mauritius, Reunion and Seychelles.

Chikungunya is generally not fatal. However, in 2005-2006, 200 deaths have been associated with chikungunya on Réunion island and a widespread outbreak in India, primarily in Tamil Nadu, Karnataka, Kerala, and Andhra Pradesh). As of September 2006, after the flood and heavy rains in Rajasthan in August 2006, India, thousands of cases were detected in Rajsamand, Bhilwara, Udaipur, and Chittorgarh districts and also in adjoining regions of Gujarat and Madhya Pradesh, and in the neighbouring country of Sri Lanka. As of October

12, 2006 in the southern Indian state of Kerala, 125 deaths were attributed to Chikungunya with the majority of the casualties reported in the district of Alapuzha [mainly in Cherthala Taluk]. In December 2006 an outbreak of 3,500 confirmed cases occurred in Maldives, and over 60,000 cases in Sri Lanka, with over 80 deaths. In October 2006 more than a dozen cases of Chikungunya were reported in Pakistan.

The main vector to humans is *Aedes aegypti* mosquitoes. Infection may be transmitted between humans in urban areas and between primates in a sylvatic cycle. Introduction of CHIKV into populated areas often results in large epidemics. Theoretically the virus could be spread through transfusion, tissue or organ transplantation

### Symptoms

The incubation period of CHIKV is between two and 10 days, with an average of two to four days. The symptoms of Chikungunya include fever which can reach 39°C, (102.2°F) a petechial or maculopapular rash usually involving the limbs and trunk, and arthralgia or arthritis affecting multiple joints which can be debilitating. In Swahili, “chikungunya” means “that which contorts or bends up”. This refers to the contorted posture of patients who are afflicted with the severe joint pain (most common feature of the disease). The symptoms could also include headache, conjunctival infection, and slight photophobia. In the present epidemic in the states of Andhra Pradesh and Tamil Nadu, India, high fever and crippling joint pain are the prevalent complaint. The fever typically lasts for two days and abruptly comes down. However, other symptoms, namely joint pain, intense headache, insomnia and an extreme degree of prostration last for a variable period, usually for about 5 to 7 days.

Most patients recover fully over a period of a few weeks, although 5 - 10% of patients will experience chronic joint pain, stiffness and swelling that can persist for a year or more.

Dermatological manifestations observed in a recent outbreak of Chikungunya fever in Southern India, Western and Eastern India includes the following:

- Maculopapular rash
- Nasal blotchy erythema
- Freckle-like pigmentation over centro-facial area
- Flagellate pigmentation on face and extremities
- Lichenoid eruption and hyperpigmentation in photodistributed areas
- Multiple aphthous-like ulcers over scrotum, crural areas and axilla.
- Lymphoedema in acral distribution (bilateral/unilateral)
- Multiple ecchymotic spots (Children)
- Vesiculobullous lesions (infants)
- Subungual hemorrhage
- Photo Urticaria
- Acral Urticaria

Histopathologically, pigmentary changes, maculopapular rash, lichenoid rash, aphthous-like ulcers show lymphocytic infiltration around dermal blood vessels (Inamadar et al). Pedal oedema (swelling of legs) is observed in many patients, the cause of which remains obscure as it is not related to any cardiovascular, renal or hepatic abnormalities.

### **Preventive measures**

The most effective means of prevention are those that protect against any contact with the disease-carrying mosquitos. These include using insect repellent containing DEET or permethrin, wearing long sleeves and pants, and securing screens on windows and doors. It's also important to empty stagnant water where mosquitoes breed

### **Advice to travellers**

There is no vaccine available to protect against CHIKV. Travellers to affected areas are advised to take insect bite precautions, particularly during daylight hours when *Aedes aegypti* mosquitoes are active.

To avoid mosquito bites:

- Wear full sleeve clothes and long dresses to cover the limbs;
- Use mosquito coils, repellents and electric vapour mats during the daytime;
- Use mosquito nets – to protect babies, old people and others, who may rest during the day. The effectiveness of such nets can be improved by treating them with permethrin (pyrethroid insecticide). Curtains (cloth or bamboo) can also be treated with insecticide and hung at windows or doorways, to repel or kill mosquitoes.
- Mosquitoes become infected when they bite people who are sick with chikungunya. Mosquito nets and mosquito coils will effectively prevent mosquitoes from biting sick people.

### **Treatment**

There is no specific treatment for Chikungunya. Vaccine trials were carried out in 2000, but funding for the project was discontinued and there is no vaccine currently available. A serological test for Chikungunya is available from the University of Malaya in Kuala Lumpur, Malaysia.

Chloroquine is gaining ground as a possible treatment for the symptoms associated with Chikungunya and as an antiviral agent to combat the Chikungunya virus. According to the University of Malaya, "In unresolved arthritis refractory to aspirin and nonsteroidal anti-inflammatory drugs, chloroquine phosphate (250 mg/day) has given promising results." Research by Italian scientist, Andrea Savarino, and his colleagues in addition a French government press release in March 2006 have added more credence to the claim that chloroquine may be effective in treating Chikungunya. The CDC fact sheet on Chikungunya advises against using Aspirin, Ibuprofen, Naproxen and other non-steroidal anti-inflammatory drugs are recommended for arthritic pain and fever.

Infected persons should limit further exposure to mosquito bites, stay indoors and under a mosquito net. Further, "supportive care with rest is indicated during the acute joint symptoms. Movement and mild exercise tend to improve stiffness and morning arthralgia, but heavy exercise may exacerbate rheumatic symptoms." Arthralgia remains to be troublesome even after 8 months.

# TYPHUS FEVERS

The typhus fevers are a group of acute infectious diseases that are caused by two species of *Rickettsia*: *Rickettsia prowazekii*, the cause of louse-borne (frequently called epidemic) and squirrel-borne typhus; and *Rickettsia typhi* (formerly, *Rickettsia mooseri*), the cause of flea-borne (or endemic) typhus. Although the clinical and pathologic pictures of these entities are similar, they differ in severity.

## ETIOLOGY

*Rickettsia* are small (0.3-0.8  $\mu\text{m}$  wide), nonmotile, coccobacilli that belong to the family Rickettsiaceae. They are not readily seen with the ordinary light microscope, staining poorly with the Gram stain, but well with Gimenez, Giemsa, Macchiavello and Castaneda stains.

Transmission electron micrographs of typhus rickettsia reveal an outer cell wall membrane (as well as a slime layer), periplasmic space, and an inner cytoplasmic membrane-characteristics of gram-negative bacilli. Muramic acid and diaminopimelic acid (also characteristic of gram-negative bacilli) are found in the cell wall; 2-keto-3-deoxyoctulosonic acid, a compound unique to gram-negative bacterial lipopolysaccharide, is present in the outer cell wall membrane. The typhus rickettsia also possesses an endotoxinlike substance that may be neutralized by specific antiserum.

The molar percent of the guanine plus cytosine (G + C) content of DNA from typhus rickettsias ranges from 28.5 to 29.7. The average size of the genome is  $10^9$  daltons. The DNA of *R. prowazekii* hybridizes consistently with the DNA from strains of *R. typhi* at a level of 70% to 77%, whereas the DNA from strains of louse-borne *R. prowazekii* hybridizes with the DNA from strains of squirrel-borne typhus at approximately 100%. Although strains of *R. prowazekii* associated with louse-borne typhus appear identical to strains associated with squirrel-borne typhus, there are minor differences.

The typhus rickettsias are obligate intracellular parasites that multiply in the cytoplasm of infected host cells. They borrow adenosine triphosphate (ATP), nicotinamide-adenine dinucleotide (NAD), and coenzyme A (CoA) from host cells. Using an adenosine diphosphate (ADP)-ATP transport system, *R. prowazekii* accumulates ATP from the environment by exchange for intrarickettsial ADP. If the environment becomes depleted of ATP, *R. prowazekii* is able to use the Krebs cycle (it possesses citrate synthase) and oxidative phosphorylation to generate ATP.

## EPIDEMIOLOGY

Louse-borne typhus may occur sporadically or in major epidemics, for example, during wars or famines when personal hygiene deteriorates and body lice (*Pediculus humanus*) flourish. After lice feed on rickettsemic patients, the ingested rickettsias multiply in the midgut cells and in 5 to 10 days appear in the feces. As lice feed, they defecate; mammals acquire infection by scratch-inoculation of feces contaminated with rickettsias through breaks in the skin. In addition, dried feces may aerosolize and lead to infection through inhalation or by direct inoculation of the conjunctivae or mucous membranes. Because lice die of their rickettsial infection, they do not serve as reservoirs.

Although the precise reservoir for louse-borne typhus is uncertain, humans appear to be at least one source. Decades after recovering from louse-borne typhus, severe stress may precipitate recrudescence disease (also called Brill-Zinsser disease); lice that feed on patients

with recrudescence may become infected and complete the louse-man-lice cycle necessary for epidemic spread.

Rickettsias virtually identical to *R. prowazekii* by DNA hybridization studies may infect the southern flying squirrel, (*Glaucomys volans*), and it is possible that flying squirrels and related rodents serve as another reservoir for *R. prowazekii*. Southern flying squirrels are nocturnal, arboreal animals that live close to humans, frequently nesting in attics or under eaves; they are highly prevalent throughout the eastern United States, Canada, and in some parts of Mexico. Numerous cases of "sylvatic" typhus have been reported in humans who had contact with these animals or their ectoparasites, especially from Virginia and the Carolinas. Thus far, all of the cases have been sporadic and not epidemic. Thus, the cycle of *R. prowazekii* infections may be maintained in nature by commensal flying squirrels and their ectoparasites-mites, fleas, and lice (squirrel lice do not feed on humans). The vector that carries squirrel-borne typhus to humans appears to be the flea, *Orchopeas howardii*. Cases of squirrel-borne typhus occur year around.

Flea-borne typhus (also called murine or endemic typhus) is transmitted to humans principally by the oriental rat flea (*Xenopsylla cheopis*), although studies in Texas suggest that the cat flea, *Ctenocephalides felis*, may also serve as a vector. Rodents of the genus *Rattus* are the principal reservoir, although other small mammals, such as shrews, may serve as reservoirs in certain parts of the world. Once the flea is infected with *R. typhi*, the organism multiplies in the midgut and is excreted in the feces. When it is feeding or biting humans, the flea defecates, and contaminated feces are inoculated into skin abrasions or bite wounds by scratching. Infections in humans are usually seasonal, occurring principally in summer and early fall, and often in persons who work or live near rat-infested buildings or sites.

In the early 1940s, 2000-5000 cases of murine, flea-borne typhus were reported annually in the United States, mostly from the Southeastern and Gulf Coast states. However, in recent years, following the institution of rat control programs, only 60 to 80 cases are reported annually, mostly from Texas.

## MANIFESTATIONS

The incubation period for the typhus fevers is generally 5 to 10 days, although the period for squirrel-borne typhus is uncertain. The clinical picture is similar for all of the typhus fevers, but the severity is variable, both within and between the groups of typhus infections. Untreated epidemic louse-borne typhus carries the highest case-fatality rate (30-70%), and flea-borne or murine typhus, the lowest (<5%).

The most prominent, early symptoms associated with all forms of typhus are fever, headache, and myalgias. The fever is remittent, seldom returning to the baseline, and is typhoidal in character with daily increases in height. Headaches begin suddenly with the onset of fever. They are unremitting, retroorbital, and bifrontal.

The clinical manifestations are protean and result from the general involvement of small vessels and capillaries. One organ may be afflicted much more than another, so that the patient may have pneumonia, renal failure, central nervous system (CNS) involvement, gastrointestinal disease, or skin rash, singly or in any combination. Although any organ may be involved, those most conspicuously affected are the skin, brain, muscles, heart, lungs, gastrointestinal tract, and kidneys. Myocarditis may occur leading to conduction disturbances and heart failure. Meningoencephalitis may give rise to seizures or a variety of neurologic deficits. The clinical findings vary enormously in kind and in range of severity: skin rash with petechiae, purpura or gangrene; muscle pain, tenderness, or rhabdomyolysis; interstitial pneumonia with oxygen diffusion defects, or acute respiratory distress syndrome (ARDS);

nausea, vomiting and diarrhea, or acute abdominal pain that may lead to surgical exploration and even resection of bowel; and microscopic hematuria or acute glomerulonephritis.

In the early stages of the illness, upper respiratory signs and symptoms resembling a viral illness may be prominent—sore throat, cough, conjunctivitis, conjunctival suffusion, pain on extraocular movement, or photophobia.

Skin rash is usually prominent, beginning on the trunk and spreading centrifugally over 1 to 2 days to involve the extremities. In louse-borne typhus, the rash progresses rapidly from macular to maculopapular, evolving quickly into petechiae, purpura or infarcts that may result in gangrene. In flea-borne or murine typhus, the rash usually remains macular and persists only for a few days, often fading before defervescence. Occasionally, some patients with murine or squirrel-borne typhus will exhibit no rash.

Recrudescent typhus (Brill-Zinsser disease) occurs years to decades following a primary attack of epidemic, louse-borne typhus. The rickettsias are latent, and any one of a variety of stresses (e.g., physical, psychosocial) may precipitate reactivation. The clinical features are similar to those of epidemic typhus, only much milder. The mortality rate is less than 5%.

Laboratory abnormalities in the typhus fevers depend on the extent of the pathology and the particular organs involved. The white blood count is usually normal, but the differential is shifted toward the myelocytic series. The serum sodium level may be low. Coagulation studies may be abnormal (usually a late finding) and show a prolonged prothrombin time and partial thromboplastin time. Decreased platelets, the presence of fibrin split products and decreased fibrinogen may signal the presence of DIC.

Hypocomplementemia (C<sub>3</sub>) commonly occurs. Microscopic hematuria may be present with an elevated serum creatinine. Meningoencephalitis, if present, may be associated with a modest pleocytosis in the cerebrospinal fluid (CSF). Elevated concentrations of circulating muscle enzymes (transaminases, creatine phosphokinase) are common. The chest roentgenogram may reveal patchy interstitial pneumonia, and the electrocardiogram may exhibit various conduction disturbances.

## DIAGNOSIS

In the early stages, the diagnosis of typhus is based on clinical and epidemiologic findings, not on laboratory tests. Isolation of rickettsias is not a normal procedure in the usual hospital laboratory and probably should not be attempted because of the risk to personnel of acquiring infection. Moreover, the requirements of inoculation of blood or tissues into the yolk sacs of embryonated hen's eggs, or into a variety of tissue culture cell lines, with incubation at 35°C, often exceeds available capabilities. Although heating and drying quickly destroy the typhus rickettsias, *R. provazekii* may remain viable for several days in blood kept at 5°C and for years after quick-freezing at -70°C.

Antigen detection techniques are not useful, and antibodies are not detectable until after a week or more of illness. Biopsies of involved skin with direct fluorescent staining of sections may be used, but the skin may be involved very little, late in the disease, or not at all. Macrophages from the blood of infected patients may be cultured and then stained for rickettsias, but this technique is not routinely available.

Serologic tests are still the mainstays for confirmation of the diagnosis. A fourfold rise in titer, comparing acute and convalescent specimens, is optimal for diagnosis, especially in areas where typhus fevers are endemic. At present, the most common serologic tests are indirect microimmunofluorescence (IFA), indirect hemagglutination (IHA), enzyme-linked immunoabsorbent assay (ELISA), and latex agglutination (LA). Because the IFA, IHA, and ELISA tests detect both IgM and IgG, these tests may be positive as early as the seventh day

of illness. In addition, if antimicrobics are used early in the disease, these tests may be positive when others are not. The Weil-Felix test (agglutination of standard strains of *Proteus vulgaris*) is seldom used because of lack of specificity, negativity in recrudescent typhus, and the late appearance of agglutinating antibodies. Despite its good specificity, complement fixation is seldom useful because it is very insensitive, and anti-complimentary activity in sera is common.

Because of the protean manifestations of the typhus fevers, the list of differential diagnoses is formidable. However, the major diseases to consider are meningococemia, infective endocarditis, septicemia, toxic shock syndrome, leptospirosis, tularemia, hemorrhagic fevers, dengue, measles, rubella, other rickettsial diseases, hypersensitivity reactions to drugs (particularly penicillin), and multisystem vasculitides, such as systemic lupus erythematosus (SLE) or other connective tissue disorders. Epidemiologic information is often extremely valuable in excluding many of these possibilities.

### **PROGNOSIS**

If treated early with appropriate antimicrobics, all forms of typhus are eminently curable. Relapse may occur if antimicrobics are discontinued prematurely (before 3-5 days). Recrudescence (Brill-Zinsser disease) occurs only with louse-borne, epidemic typhus, but recovery is usual.

Delayed or untreated louse-borne, epidemic typhus carries a mortality rate of 30% to 70%, whereas, murine or flea-borne typhus carries a mortality rate of less than 5%. In general, the extent of recovery is directly proportional to the amount of damage sustained by organs during the infection. For example, gangrene of the extremities may be severe, resulting in loss of digits. Encephalitis, if diffuse and severe may result in permanent brain damage, often expressed as retarded learning or inability to return to earlier occupations.

Immunity after infection is generally solid and long-lasting. However, early interruption of the disease with antimicrobial therapy may diminish the immune response and decrease protection. Excellent cross immunity and protection exists between louse-borne and flea-borne typhus.

### **THERAPY**

The antimicrobics of choice for all rickettsioses are chloramphenicol or the tetracyclines. When these agents are used early in the disease, the results are excellent.

In the seriously ill patient who may be comatose or delirious, chloramphenicol is preferred because of ease of administration (IV or PO), good diffusibility into virtually every tissue, and penetration into cells. Adults and children with serious infections may be given 50 to 60 mg/kg body wt/day, intravenously, in four equal portions, 6-hourly. With improvement, treatment may be continued using the same regimen except for change to peroral administration. Treatment should be continued for 5 days after defervescence.

The tetracyclines are also highly effective and are ideal for the patient who is alert and cooperative, and can take medications perorally. Adults treated with tetracycline may be given as much as 500 mg every 6 hours. Although the recommended peroral dose in children over age 8 years is 25 to 50 mg/kg of body wt/ day, given in four equal portions, 6-hourly, the intravenous dose for such children should not exceed 10 to 20 mg/kg body wt/day given in four equal portions, 6-hourly. Again, therapy should be continued for 5 days after defervescence. Pregnant women, premature infants, and children up to 8 years of age should not be treated with any of the tetracyclines (if essential, the number of days of treatment should not exceed 3) because the tetracyclines permanently discolor teeth and interfere with the development of bones. The tetracyclines are highly irritating and often cause

thrombophlebitis when injected intravenously. Absorption after peroral administration may be hampered by ingestion of dairy products and any other substances rich in divalent cations.

Nonspecific measures of management include: careful attention to fluid and electrolytic balance, with caution not to overhydrate and produce dilutional hyponatremia (a particular hazard in patients prone to seizures from encephalitis); seizure control in those with seizures; and early treatment of heart failure or shock to maintain perfusion of vital organs. The value of the routine use of glucocorticoids for vasculitis is not established; however, in special circumstances, for example, when vasculitis threatens the arterioles of vital organs, they may be beneficial. Management of DIC is particularly difficult, because infusions of platelets or fresh frozen plasma may possibly accentuate the condition. Nevertheless, if uncontrollable bleeding occurs, use of such products may be necessary.

## PREVENTION

Outbreaks of louse-borne typhus may be effectively controlled by delousing, louse control, immunization, and in special circumstances, with antimicrobial prophylaxis.

Delousing is best achieved by applying insecticide dust to clothing. Although DDT (10%) rapidly kills both adult lice and hatching larvae, resistance to its use is common. Other agents are lindane (1% gamma HCH), malathion (1%), temephos (2%), and the carbamates. Louse susceptibility testing may be carried out with kits from the World Health Organization and should be performed prior to use of delousing agents. Louse control in endemic populations at high risk is more difficult, and insecticides must be complimented by public education and improvement in hygiene and standards of living.

Immunization against louse-borne typhus is possible using a vaccine containing the attenuated E strain of *R. prowazekii*; however, the vaccine is not readily available and is not without adverse reactions. Newer, highly purified vaccines, using immunogenic portions of *R. prowazekii* through genetically engineered constructs, appear promising. Chemoprophylaxis with the long-acting tetracyclines should be used only under special circumstances, for example, in high-risk persons poorly protected by vaccines (immunodeficiency) or in those for whom vaccines and louse control are not available or effective. The tetracyclines should be avoided as prophylaxis in small children because bone and teeth may be adversely and permanently damaged.

Control of flea-borne or murine typhus relies solely on rat and flea control, generally through rodenticides and insecticides. Vaccines are not available for flea-borne typhus. Chemoprophylaxis is unwarranted because the mortality from untreated infection is less than 5%, and epidemics do not occur.

## SCHISTOSOMIASIS

Schistosomiasis is a disease complex caused by the adult forms of long-lived flukes (trematodes) that belongs to the genus *Schistosoma* and resides within the venous plexuses of mammals. The illness may be acute or chronic and slowly progressive, reflecting the response of the host to the continuing intravascular deposition of eggs and to the continued elaboration of excretions by the worms. Schistosomiasis is usually attributed to three species of schistosomes, subdivided into intestinal (*Schistosoma mansoni* and *Schistosoma japonicum*) or urinary (*Schistosoma haematobium*) types, according to the site preferred by the adult worms. This schema is useful but simplistic. Other species infect humans: *Schistosoma mekongi*, *Schistosoma intercalatum*, and *Schistosoma matthei*.

Moreover, the preferred sites of involvement are relative rather than absolute; for example, eggs of *S. haematobium* are commonly found in the rectal mucosa of an infected person, and in infections with *S. mansoni*, eggs may appear sporadically in the urine.

## ETIOLOGY

The adult schistosomes are delicate cylindrical worms that are 1 to 2 cm in length and adapted for existence in venules. They differ from other trematodes in that the sexes are separate; two longitudinal outfoldings of the male form a gynecophoral canal in which the filiform female is clasped in copula. Although the species differ morphologically, this fact is not clinically important because a specific diagnosis is derived from the characteristic shape of eggs recovered from the urine, feces, or infected tissues

## EPIDEMIOLOGY

Humans are infected with schistosomes through contact with water containing the infective larval stage, the free-swimming cercariae, which penetrate the skin or mucous membranes. The cercariae are 0.4 to 0.6-mm long, fork-tailed organisms derived from infected aquatic or amphibious snails. Snails become infected only if eggs of schistosomes passed in the urine or feces of the infected mammalian host reach fresh water and hatch. The minute, free-swimming miracidium thus released lives only a few hours unless it contacts and promptly penetrates a snail suitable as an intermediate host. In this essential intermediate host, the parasite undergoes extensive multiplication within the tissues so that a single infected snail may shed thousands of cercariae into the water over a period of many weeks.

The parasite-snail interaction is highly specific, and only a few species of snail support the cycle. The geographic distribution of schistosomiasis is, therefore, peculiarly focal. For example, appropriate snails are present in Puerto Rico but not in the Virgin Islands or Cuba. They are not present in the United States.

Adult schistosomes are less host specific. Mammals other than humans may serve to a variable degree as definitive hosts and maintain the parasite. *S. japonicum* is the extreme example; in endemic areas, high rates of infection may be found in dogs, cats, rats, and cattle—a factor that complicates control of the disease.

The global pattern of schistosomiasis is determined by the distribution of snails appropriate as intermediate hosts, the pattern of discharge into fresh water of egg-containing feces or urine, and the water contact habits of humans. Aptly termed a man-made disease, schistosomiasis increases in frequency of occurrence as man-made lakes and irrigation systems are developed in tropical regions.

Manson's schistosomiasis is the only form that occurs in the Western Hemisphere. It is confined to Puerto Rico and some islands in the Lesser Antilles and to northern South America in Brazil, Surinam, and Venezuela. *S. mansoni* also occurs across central Africa, in the Nile Valley, in Madagascar, and in Yemen. *S. haematobium* is distributed throughout much of Africa and in some Middle Eastern countries; there is also a focus in India. Control measures have eliminated transmission of *S. japonicum* in Japan, but the helminth is endemic in parts of the Philippines, China, and Indonesia. A related species, *S. mekongi*, occurs in Kampuchea and Laos. Intestinal schistosomiasis is caused by *S. intercalatum* in six central African countries.

In endemic areas, more than 90% of adults may be infected. The intensity of infection (i.e., the number of worms per person) is of epidemiologic and clinical import. The worm burden can be indirectly estimated in children or in recent infections in adults by counting the

eggs passed in the urine or feces. Older children and young adolescents characteristically constitute the age-group that excretes the greatest number of eggs in endemic areas.

## **PATHOGENESIS AND PATHOLOGY**

Cercarial proteolytic secretions aid rapid penetration of the skin; in the process, the cercariae lose their tails and become schistosomules that measure 0.1 mm to 0.2 mm in length. Some of the larvae are trapped in the skin of previously sensitized persons, inducing a papular pruritic eruption. In the inexperienced host, the majority of the schistosomules move into the lymphatics and venules and migrate through the pulmonary capillary filter. Schistosomules feed on blood and grow rapidly in the intrahepatic portal venous system. Those of *S. mansoni* and *S. japonicum* then migrate into the distal branches of the superior and inferior mesenteric veins around the intestine and rectum, and those of *S. haematobium* migrate through the hemorrhoidal and pudendal veins into the vesical and pelvic plexuses. By this time the worms have mated, and egg laying begins 5 to 12 weeks after cercarial penetration, varying with the species.

The young adult schistosomes rapidly acquire host-derived antigenic materials on their body surfaces and are thus immunologically camouflaged. Humans do not react to the living worms per se, but the secretions and excretions of the worms may engender hypersensitivity and general manifestations of illness.

The most important pathologic consequences of schistosomiasis are egg associated. Because each female worm may lay eggs for years, the disease is slowly progressive. Eggs are deposited in the small venules of the intestines or genitourinary organs; some are trapped locally, and others move in the venous stream and lodge at the first sinusoidal or capillary filter (i.e., the liver or the lungs). Viable miracidia within eggs produce toxic and antigenic products that pass through the shells to cause minute abscesses wherever the eggs lodge. An initial acute inflammatory infiltrate with numerous eosinophils is replaced by round cells, *giant* cells, and epithelioid cells that accumulate around each egg. Fibroblastic activity follows, yielding minute, egg-centered, granulomatous pseudotubercles, the typical defense mechanism of the sensitized host.

In heavy infections, masses of eggs may produce confluent ulcerations in the intestinal mucosa, resulting in an acute schistosomal dysentery, or in the urinary bladder mucosa, causing an acute hemorrhagic cystitis. Only a small percentage of the eggs that are laid escape in the feces or urine. Those trapped locally induce a fibrotic, irregular thickening of the bowel or bladder wall and formation of abscesses and papillomatous growths. Strictures, adhesions, and fistulas may develop. In infections with *S. haematobium*, calcified eggs may accumulate in the bladder wall, functional impairment of the bladder and ureters develops, and hydro-nephrosis is common. Additionally, the pelvic genital organs are usually involved.

Although morbidity is associated with lesions in the intestinal or urinary tract, mortality often reflects circulatory dysfunction resulting from the progressive fibrosis engendered in the liver or the lungs in response to trapped, embolic eggs. Hepatomegaly, especially with enlargement of the left lobe, may develop rapidly. In the liver, extensive periportal and perilobular fibrosis occurs; the end result is the so-called Symmers' pipe-stem fibrosis-grossly-observable white accumulations of fibrotic tissue. An early hyperplasia of splenic reticular tissue is followed by diffuse fibrosis. Portal hypertension may follow, with marked splenomegaly. Collateral vascular pathways become functional, and some eggs are thereby shunted directly to the lungs. In one series of autopsies, one-third of the deaths associated with Manson's schistosomiasis resulted from bleeding from a collateral varix. With *S. haematobium*, the lungs are the primary filter for embolic eggs; pulmonary hypertension with cor pulmonale and right-side failure may be an end result.

Chronic intestinal schistosomiasis may be associated with lesions in the kidney. Glomerulosclerotic changes in infected patients may be the result of deposition of specific schistosomal immune complexes. Antigenic materials elaborated by the worms are demonstrable in the blood and urine of infected persons.

In areas where infections caused by both *Salmonella* spp. and *Schistosoma* spp. are endemic, there may be a synergistic relationship. Patients with urinary schistosomiasis may be urinary carriers of *Salmonella typhi*. Patients with hepatosplenic schistosomiasis may exhibit a chronic salmonellal bacteremia. Morphologic studies have shown that the bacteria are intimately associated with the worms. Elimination of the schistosomal infection is required before the bacteremia will respond to chemotherapy.

## MANIFESTATIONS

The clinical picture of each of the several types of schistosomiasis depends on the intensity of infection (i.e., the number of worms harbored) and on poorly understood variables in the response of the human host. At one end of the spectrum, an infected individual may be asymptomatic, as was emphasized by a study of schistosomiasis in 173 expatriots returning to England. In endemic areas, a significant percentage of infected indigenous people are symptom free.

However, the evolution of symptoms in an endemic area also is related to the intensity of infection; in a population with Manson's schistosomiasis followed over a 3-year period in Brazil, there was a high prevalence of hepatomegaly (over 80%) and splenomegaly (over 15%), as contrasted to rates of 10% and 1%, respectively, in a nonendemic control area. Over the 3 years, there was spontaneous regression of hepatomegaly in 13% and splenomegaly in 56%-phenomena most common in older persons with light infections. Those with heavy infections (i.e., 500 or more eggs per gram of feces) had an excess risk of splenomegaly of 19.6%, and of persistence of 61.5%.

In heavily infected patients, a sequence of events occurs. Cercarial penetration may or may not induce a papular eruption. Three to 6 weeks later, symptoms similar to serum sickness develop: fever, urticarial rashes, malaise, muscle aches, headaches, diarrhea, cough, and weight loss, commonly with eosinophilia. Thereafter, in heavy infections with *S. mansoni* and *S. japonicum*, bloody diarrhea, abdominal pain, and hepatosplenic enlargement are characteristic findings. This acute process is rarely life threatening. After months or years of continued deposition of eggs, intestinal strictures and papillomatous growths may appear. Accumulation of eggs in the liver leads to portal hypertension and congestive splenomegaly, and, after the development of collateral venous channels, to pulmonary lesions. Death is secondary to portal or pulmonary hypertension; ascites, inanition, hematemesis from ruptured esophageal varices, and heart failure are common terminal events.

With infections caused by *S. haematobium*, bladder involvement, with intermittent terminal hematuria, dysuria, and frequency, is characteristic. Progressive deposition of eggs may produce ureteral obstruction with a resulting hydronephrosis or pyelonephrosis. Egg-associated lesions may involve various elements of the male and female genital tracts.

Ectopic egg deposition, particularly in the central nervous system, may produce serious complications. In infections with *S. japonicum*, seizures caused by cerebral involvement are recognized sequellae. A necrotizing myelitis may be caused by *S. mansoni*.

## DIAGNOSIS

For the diagnosis to be considered, the patient must have been in a region where schistosomiasis occurs. Most infections follow contact with natural or impounded bodies of

water in rural areas. However, foci of transmission may occur within tropical cities in endemic areas, as in uncontrolled swimming pools or, rarely, even in a motel bathtub.

Schistosomiasis may be diagnosed with certainty only by the microscopic demonstration of the characteristic eggs. Because excretion of eggs may be scanty, or absent during the early phases of illness, it is essential that repetitive examinations be done using appropriate concentration techniques. The eggs of *S. mansoni* and *S. japonicum* should be sought by microscopic examination of fecal sediments obtained after processing by a procedure such as the formalin-ether concentration method. The intensity of infection may be assessed by averaging the results of repetitive fecal egg counts done by the Kato thick smear method. The eggs of *S. haematobium* are passed in the urine with a diurnal periodicity, with peak excretion occurring between midmorning and midafternoon. The eggs in urine collected during this period may be concentrated by simple sedimentation in a conical container or by passing the urine through a cellulose filter; quantification of egg output is obtained by counting eggs collected on a membrane filter after processing a known volume of urine, usually 10 ml. If schistosomiasis is suspected and repeated examinations of feces and urine are negative, then proctoscopy or cystoscopy with biopsy of mucosal lesions is justified; microscopic examination of the tissue fragments after compression will reveal eggs if they are present.

A number of immunologic diagnostic procedures have been introduced; some are available through the Centers for Disease Control. Although such tests are useful, problems of sensitivity and of specificity have not been completely resolved. A suggestive report should be confirmed by demonstration of eggs.

In the initial phase of a severe infection, the high fever, prostration, cough, headache, muscle aches, and abdominal pain may suggest typhoid or other bacteremic states; a developing eosinophilia is then a useful diagnostic clue. With the onset of deposition of eggs by *S. mansoni*, or particularly *S. japonicum*, intestinal involvement may be blatant, with an acute dysentery that requires differentiation from shigellosis, amebiasis and ulcerative colitis. At the other extreme, if few worms are present, there may be little change in bowel habits. Gross hematuria, with or without symptoms of cystitis, is the characteristic sign of a developing infection with *S. haematobium*. A history of travel in an endemic area and the presence of eosinophilia should lead to a search for eggs.

## PROGNOSIS

The course of untreated schistosomiasis is variable. The immune responses of the host, the intensity and timing of infection and of reinfection, and possibly the strain of parasite are ill-defined determinants. In the competent host, immunomodulation may occur and the granulomatous response around newly deposited eggs in tissues is less pronounced with the passage of time. As was demonstrated in Puerto Rico, some infected persons may pass numbers of eggs for years in the absence of related signs or symptoms. However, in most endemic areas patients are commonly seen with the consequences of slowly progressive schistosomiasis-severe portal or pulmonary hypertension or obstructive uropathy.

With currently available drugs such as praziquantel, remarkable improvement may be obtained on treatment; the obstructive uropathy caused by *S. haematobium* or seizures from cerebral involvement with *S. japonicum* may disappear. However, therapy cannot be expected to reverse established fibrotic changes resulting from a long-term infection.

## THERAPY

Treatment has been revolutionized with the introduction of safe, effective, peroral schistosomicidal drugs. The intelligent use of these compounds requires knowledge of the species and geographic origin of the schistosome involved and of appropriate techniques for quantitating the effectiveness of therapy. Whether light infections should be treated is a matter of dispute. However, treatment will eliminate the possibility of ectopic deposition of eggs, and this consideration alone favors the treatment of all cases.

Three drugs are now widely used: praziquantel, oxamniquine, and metrifonate. Praziquantel (Biltricide), a heterocyclic pyrazinoisoquinoline compound, is a broad-spectrum anthelmintic that is effective against all species of schistosomes that infect humans and is the drug of choice. Therapeutic concentrations cause muscle contraction, immobilization of the worms, and vacuolization of the tegumental coating, exposing the worms to attack by phagocytic cells. At the recommended dosage of 20 mg/kg of body wt, PO, every 4 hours, for three doses, cure rates of 70% to 100% are achieved with all forms of schistosomiasis. Side effects of treatment are generally mild, consisting primarily of abdominal pain, nausea, diarrhea, headache, and dizziness.

Oxamniquine (Vansil) is a tetrahydroquinoline compound that is active only against *S. mansoni*. The drug inhibits synthesis of DNA and RNA in the parasite. In South America, patients with Manson's schistosomiasis respond to a single oral dose of 15 mg/kg body wt; in Africa, equivalent results require one to two doses of 30 mg/kg body wt. Oxamniquine has been used extensively in mass control programs without serious side effects, although hallucinations, epileptiform seizures, and electroencephalographic changes have been recorded. In Brazil, resistant infections have been encountered.

Metrifonate (Bilarcil) is inexpensive and widely used in endemic areas for the treatment of infections with *S. haematobium*; it is not effective against other species and is not available in the United States. An organophosphorus ester, metrifonate is a cholinesterase depressant. In practice, 7.5 mg to 10 mg/kg body wt doses are given at 14-day intervals for a total of three doses; the spacing permits recovery of depressed cholinesterase levels.

## PREVENTION

Persons planning travel to regions in which schistosomiasis is endemic should be warned of the hazard associated with swimming or wading in fresh water. No chemoprophylaxis is available. In organized societies, effective control can be achieved by prevention of contact by humans with infected water, collection and treatment of egg-containing excreta, and control of vector snails through environmental engineering or through the use of molluscicides.

## REMAINING PROBLEM

The advent of the new perorally administrable schistosomicidal drugs has revolutionized the treatment and control of schistosomiasis. However, strains of *S. mansoni* resistant to oxamniquine have already been identified in nature, and resistance has been induced in the laboratory. Will praziquantel and newer compounds on the horizon suffer the same fate? Evidence continues to accrue indicating that a relative immunity develops in persons exposed repeatedly. However, little is known of the determinants leading to the regression or progression of the morbid process. Answers may derive from the current application of the techniques of molecular biology. The identification of schistosomal antigens should provide more sensitive and specific serodiagnostic tests and may also lead to vaccines to enhance host immune defenses.

# LEPROSY

Leprosy is a disease that results from infection with *Mycobacterium leprae* in a small proportion of humans exposed to and presumed to be infected with this microorganism. The disease is chronic, ordinarily progresses if untreated, and exhibits a broad spectrum of manifestations, ranging from the limited process in patients with a brisk immune response (tuberculoid leprosy) to the disseminated disease characteristic of patients with a minimal response (lepromatous leprosy). Although *M. leprae* was considered pathogenic only for humans, a similar process, associated with an organism indistinguishable from *M. leprae*, was encountered among armadillos captured in Louisiana and contiguous portions of Mississippi and Texas.

## ETIOLOGY

*Mycobacterium leprae*, the etiologic agent of leprosy, is an acid-fast bacillus. After fixation and staining by standard techniques, viable *M. leprae* stain both brightly and uniformly. Dead bacilli stain irregularly and usually predominate in material obtained from lesions, accounting for the frequent description of the organism as pleomorphic. Leprosy bacilli have not been cultivated in cell-free media and have not been grown consistently in cell cultures.

The optimal temperature for multiplication of *M. Leprae* is lower than 37°C. This is consistent with the predilection of lesions to form on the cooler parts of the body, and with the limited multiplication of the organism that occurs after local inoculation into the footpads, ears, and testes of normal mice, but not after inoculation into more proximal or less superficial tissues. In the hind footpad of immunologically competent mice, following the inoculation of 5000 organisms and a lag phase of indeterminate duration, *M. Leprae* multiply to a maximum of 1 to 2 million bacilli in the course of 4 to 6 months, with a doubling time during logarithmic growth of 11 to 14 days. Thereafter, the number of organisms changes very little, while the viable organisms are killed as the mouse mounts an effective cell-mediated immune response. Gross lesions of the footpad are never seen. In contrast, gross lesions occur regularly in experimentally infected nude mice—the ability of immunosuppressed rodents to limit multiplication of *M. leprae* is impaired.

## EPIDEMIOLOGY

According to estimates of the World Health Organization, the present total of patients with leprosy exceeds 10 million (10-15 million). Only 3.7 million of these are registered. The majority reside in Southeast Asia, India, sub-Saharan Africa, and Latin America.

Progress in understanding the epidemiology of leprosy has been obstructed by inability to cultivate *M. Leprae* in vitro and by the tenacious doctrine that leprosy is feebly contagious and transmitted only by prolonged, direct skin-to-skin contact.

Untreated and relapsed patients with multibacillary (i.e., lepromatous and near-lepromatous) leprosy are the most important sources of infection. Such patients may have extensive involvement of the nasal mucous membranes with consequent shedding of large numbers of viable *M. leprae* in the sputum and nasal secretions. Moreover, leprosy bacilli may survive outside the body for days. In fact, there appears to be a close analogy between leprosy and tuberculosis in terms of the numbers of organisms broadcast into the environment, and the attack rates among contacts. A few cases of transmission by injection (by presumably contaminated tattoo needles) have been recorded. The possibility of an

arthropod vector was suggested by the recovery of viable *M. leprae* from mosquitos and bedbugs permitted to feed on untreated patients with lepromatous leprosy, but infection of humans by the bites of these arthropods was not demonstrated. The existence of healthy carriers has been claimed, but no evidence of their infectiousness has been produced. No nonhuman reservoir of infection is known; although infection of feral armadillos with *M. leprae* is known, no association between contact with armadillos and human leprosy has been demonstrated. Thus, *M. leprae* is probably transmitted by the respiratory route.

The factors that determine who will exhibit clinical leprosy are not known. Intercurrent viral infections may increase susceptibility to *M. leprae*; thus, an epidemic of leprosy occurred on the Pacific island of Nauru shortly after the conclusion of World War I, following pandemic influenza in which 30% of the islanders died. Currently, there is also interest in the possibility that susceptibility to leprosy may be HLA-linked.

## **MANIFESTATIONS**

### **Indeterminate Leprosy**

The earliest clinical manifestation of leprosy is one or more ill-defined, hypopigmented, hypesthetic macules. These lesions may not be immediately recognized in nonendemic areas unless the physician is alerted by a history of contact. The histopathologic features of such macules are not diagnostic, unless involvement of dermal nerves or the presence of acid-fast bacilli (typically only a few) can be demonstrated.

### **Tuberculoid Leprosy**

The sparse lesions of polar tuberculoid leprosy are macular or raised and usually display loss of pigmentation, sweating, and tactile sensation. A dermal nerve may be palpable near the lesion, and characteristically there is tender induration of a major peripheral nerve serving the area of the lesion. The lesions of borderline tuberculoid leprosy resemble polar tuberculoid lesions, but are usually multiple and smaller. Enlarged cutaneous sensory nerves are less commonly found, but enlargement of major peripheral nerves is common.

### **Borderline (Dimorphous) Leprosy**

The lesions of borderline leprosy differ from tuberculoid lesions in that they are more numerous, symmetrically distributed, and erythematous or hypopigmented. The characteristic borderline lesion is circular, with a raised, fairly well defined, erythematous margin and an atrophic, hypesthetic center. Enlargement of peripheral nerve trunks may be widespread.

### **Lepromatous Leprosy**

The skin lesions of lepromatous leprosy consist of numerous, symmetric, small, hypopigmented macules or erythematous papules. Nodules develop later in the course of the disease and, even later, the skin becomes diffusely infiltrated and thickened. Characteristic late lesions include enlarged, sometimes pendulous ear lobes; thinned eyebrows, eyelashes, facial and body hair; and destruction of the nasal cartilages with obstruction of the nasal passages and typical deformity of the nose. Nerve damage is diffuse and symmetric, involving dermal nerves and nerve endings more than major nerve trunks. The features typical of advance lepromatous leprosy are summarized in Table 1.

## Peripheral Nerves

Damage to peripheral nerves leading to loss of sensation, deformity, and mutilation is characteristic of leprosy. Patterns of damage vary across the spectrum of leprosy. Toward the tuberculoid pole, the process usually involves the superficial portions of one or more major nerves asymmetrically. Toward the lepromatous pole, the process is usually more diffuse and symmetric, involving smaller ramifications of sensory nerves and the sensory endings themselves.

## DIAGNOSIS

The diagnosis of leprosy rests on the demonstration of *M. leprae* in association with characteristic histopathologic changes; it is established by histopathologic examination of tissue obtained by biopsy of a lesion. The biopsy specimen should include all of the layers of the skin. If properly prepared sections are stained with a standardized, room temperature, acid-fast stain, acid-fast bacilli will be found. The number of bacilli may be very small in polar tuberculoid and indeterminate forms of the disease, requiring intensive search of many sections. Histopathology in any way suggestive of leprosy should lead to the preparation of sections stained for acid-fast bacilli. The diagnosis of leprosy should never be excluded *a priori* because of the absence of a history of a contact.

## PROGNOSIS

Indeterminate leprosy probably heals spontaneously without important residua in most patients. However, antimicrobial treatment is required to limit disability in both tuberculoid and lepromatous forms and to reverse the infectiousness of patients with multibacillary leprosy. Effective antimicrobial therapy makes it possible to arrest clinical progression in the majority of patients.

The lepromin skin test is useful for the classification of patients in the spectrum of leprosy and for prognosis. Lepromin, an autoclaved homogenate of lepromatous tissue, is injected intracutaneously and the reaction is usually read after 3 or 4 weeks; a papule larger than 3 mm in diameter is considered to be a positive reaction. The lepromin test is negative in near-lepromatous and polar lepromatous leprosy, and positive toward the tuberculoid pole of the spectrum. Its prognostic value rests on the belief that indeterminate leprosy is thought to be less likely to evolve to lepromatous leprosy if there is a reaction to lepromin. Generally, the larger the reaction, the closer the patient is to a tuberculoid state—a more benign form of the disease. *The lepromin test is not a diagnostic test.* Because lepromin contains human histocompatibility antigens, most normal adults react. Moreover, “lepromin” prepared from normal skin provokes reactions that are similar to, but smaller than, those evoked by standard lepromin.

**Table 1. Clinical Features of Advanced Lepromatous Leprosy**

Site	Symptoms
Skin	Symmetrically distributed macules, papules, plaques, and nodules (lepromas); loss of eyebrows (especially outer third) and eyelashes; rarely, loss of scalp hair; leonine facies (accentuation of features by infiltration and nodules); thickened pendulous ears; spider telangiectases; edema of extremities (invasion of lymphatics)
Eyes	Conjunctival and episcleral nodules;

Upper respiratory mucous membranes	beading of corneal nerves; superficial punctate keratitis, interstitial keratitis with pannus formation; chronic plastic iridocyclitis Nasal stuffiness, coryza, epistaxis (infiltration of mucous membrane); ulcers of uvula and tonsils, loss of teeth (oropharyngeal infiltration); septal perforation, nasal collapse (destruction of cartilaginous septum), hoarseness, stridor, asphyxia (laryngeal infiltration)
Other organs/systems	Hepatomegaly, splenomegaly, lymphadenopathy, testicular invasion and destruction, gynecomastia, cystic bone changes in the distal phalanges, and skeletal muscle invasion. Kidneys are spared in the absence of immune complex nephritis or amyloidosis.
Serum	Hypergammaglobulinemia (polyclonal), elevated immunoglobulins (especially IgG), biologic false-positive serologic tests for syphilis, antithyroglobulin antibody, rheumatoid factor, positive lupus erythematosus cell preparations, cryoglobulinemia.

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## THERAPY

### Antimicrobial Therapy

Specific antimicrobial therapy for leprosy began in 1941, with the administration of glucosulfone (promin) at the National Hansen's Disease Center in Carville, Louisiana. In the course of the next 20 years, during which time response to treatment could be assessed only by observing changes in the clinical status and the density of acid-fast bacilli in scrapings of lesions, virtually all patients were observed to respond well to treatment with the sulfones-dapsone (4,4'-diaminodiphenylsulfone, DDS) and related drugs. Leprosy workers were alert to the possibility that treatment with a single drug might lead to the emergence of drug-resistant *M. leprae*, with consequent relapse. However, relapses were noted to be infrequent among patients who continued treatment for long periods, and monotherapy with dapsone for many years, if not for life, won recognition as definitive treatment.

The explanation for the success of monotherapy with dapsone emerged only after 1960, when a technique was described for growing *M. leprae* in the footpad of the mouse. The MIC was found to be 1 to 3 ng/ml, some 500-fold less than the concentrations of dapsone in plasma and tissues that resulted from the standard dose of 100 mg/day. However, in 1964, again employing the mouse-footpad technique, researchers demonstrated dapsone-resistant *M. leprae* in several patients with lepromatous leprosy in relapse despite many years of supervised monotherapy with dapsone in full dosage.

During the next decade, a number of drugs were evaluated by administering the drugs individually to previously untreated or relapsed patients with lepromatous leprosy and, at intervals, inoculating mice with *M. leprae* recovered from specimens obtained by biopsy of skin lesions. Clofazimine, the thioamides-ethionamide and prothionamide and rifampin, as well as dapsone, were shown to be bactericidal; organisms recovered from biopsy specimens failed to multiply in mice after treatment with dapsone for an average of 100 days, or a few days after a single 600 mg to 1500 mg dose of rifampin. However, the footpad of the mouse is a relatively insensitive culture medium. Immunologically normal mice may be inoculated

with no more than  $10^4$  *M. leprae* per footpad, and failure of the organisms to multiply means only that the proportion of the viable *M. leprae* is smaller than  $1:10^4$ .

A new patient with lepromatous leprosy may well carry  $10^{11}$  *M. leprae*, of which no more than  $10^{10}$  are viable by morphologic criteria; after 3 months of treatment with dapsone, infectivity for normal mice is lost, although more than  $10^7$  (but  $<10^8$ ) viable *M. leprae* could still be present in the patient. Using immunosuppressed mice permits a larger inoculum, reducing the threshold for detecting viable *M. leprae* to about 1 in  $10^5$  organisms; as a result, the persistence of viable, fully drug-susceptible *M. leprae* was demonstrated in the tissues of patients after treatment with dapsone for 10 years, rifampin for 2 to 5 years, and dapsone plus rifampin for 6 months. Patients with paucibacillary leprosy harbor much smaller populations of *M. leprae*, and the risks that such patients will relapse with drug-resistance or harbor persisting organisms are negligible.

During the past 10 to 15 years, sparked by the demonstration of dapsone-resistant *M. leprae* in previously untreated patients, treatment with regimens of combinations of bactericidal drugs has gained acceptance, both for management of the individual patient, and for control of leprosy. Originally, it was hoped that some combination of available drugs might prove effective in eradicating persisting *M. leprae*. However, it appears that the combination of daily rifampin, clofazimine, and dapsone is no more effective in this respect than is an initial large dose of rifampin followed by daily dapsone monotherapy. On the other hand, despite the continuing deficient specific immune response, persisting *M. leprae* do not inevitably cause relapse of lepromatous leprosy among patients whose treatment has been terminated.

The risks of relapse caused by the emergence of drug-resistant *M. leprae* and the persistence of viable organisms have dictated the development of practical, combined-drug regimens of finite duration that will prevent relapse of multibacillary leprosy. Such regimens are essential to the control of leprosy in regions where the disease is endemic. For leprosy control programs, the World Health Organization suggests a practical, combined-drug regimen consisting of daily, self-administered 100-mg doses of dapsone and 50-mg doses of clofazimine, supplemented with monthly, supervised 600-mg doses of rifampin and 300-mg doses of clofazimine. This regimen is recommended for at least 2 years, and preferably until acid-fast bacilli are no longer demonstrable in smears. This regimen includes three bactericidal drugs; it appears to be safe and is reasonably cheap. It should be effective and should prevent relapse with drug-resistant bacilli, even in patients whose *M. Leprae* are resistant to dapsone. This same regimen should also be useful for the treatment of patients with multibacillary leprosy in nonendemic regions. In this situation, clofazimine may be less well accepted because of the pigmentation that may accompany its use. Either ethionamide or prothionamide, administered in a daily oral dose of 375 to 500 mg, may be substituted for clofazimine. However if either of these is administered, monitoring of liver function is required.

For paucibacillary leprosy, the World Health Organization has recommended a short-course, combined-drug regimen: daily, self-administered 100-mg doses of dapsone for 6 months, supplemented by six monthly, supervised 600-mg doses of rifampin.

## PREVENTION

Leprosy is best prevented by blocking transmission of *M. leprae* in the community. Isolation of patients presumed to be infectious is illogical as a preventive measure; chemotherapy renders patients noninfectious so rapidly that nothing is achieved by isolation. Dapsone monotherapy is not curative, and lifelong maintenance of suppression is not feasible in many areas. The ability of the regimen recommended by the World Health Organization to control leprosy is currently under study. Leprosy may also be prevented by prophylactic

antimicrobial therapy. Logically, only the subclinically infected should be treated; however, because they cannot be identified with certainty, the entire community must be treated. Single, large doses of rifampin may be expected to be effective in chemoprophylaxis.

No vaccine is currently available for the prevention of leprosy.

### REMAINING PROBLEMS

A vaccine prepared from heat-killed *M. leprae* is under study. The immense numbers of bacilli required are obtained from experimentally infected armadillos.

Cultivation of *M. Leprae* in vitro remains an elusive goal. However, recent progress in the molecular biology of *M. leprae* may offer alternative sources of specific antigens to be employed as vaccines and disclose enzyme systems that are suitable targets for new drugs.

## PLAGUE

Plague normally involves a three-way interaction between *Yersinia pestis*, wild rodents, and fleas parasitic on the rodents. *Yersinia pestis* gains entry into humans by accident; if infection occurs, it is virtually equivalent to disease—usually manifest as bubonic plague. Other clinical forms include pneumonic, septicemic, meningial, and pharyngeal plague.

### ETIOLOGY

*Yersinia pestis*. Named, following a reorganization of nomenclature in 1971, after Alexandre Emile-Jean Yersin, the first investigator positively to identify the organism, during the Hong Kong outbreak of 1894. Previously, the bacillus was known as *Pasteurella pestis*.

*Yersinia pestis* is a plump (0.5-0.8 X 1.5-2  $\mu\text{m}$ ), gram-negative, nonmotile, nonsporulating, nonlactose-fermenting, pleomorphic bacillus. A bipolar or safety-pin appearance is best demonstrated in smears of infected animal tissues stained by Giemsa's or Wayson's method. This classic appearance is not dependably evident in preparations stained by Gram's method. The plague bacillus is identified by (1) its characteristic appearance in broth and agar cultures; (2) its staining characteristics; (3) lysis by specific bacteriophage; (4) the agglutination reaction; (5) fluorescent antibody (FA) staining; and (6) necropsy findings after inoculation into susceptible laboratory animals. Although biochemical reactions can be used to differentiate *Y. pestis* from *Y. pseudotuberculosis*, bacteriophage testing is highly specific and can be applied more rapidly.

Plague bacilli are aerobic and facultatively anaerobic. They are not fastidious and grow readily in most bacteriologic culture mediums. However, growth is slow even at the optimum temperature of 28°C and requires about 48 hours before colonies are readily discernible on plain agar; growth is satisfactory at 35°C to 37°C. Colonies are small (1-3 mm in diameter) and grayish, with a granular or beaten-copper surface best seen with a 3- to 10-power lens. After 24 hours at 28°C in standard broth medium examined without shaking, plague bacilli exhibit a flocculent type of growth without turbidity.

The FA test is based on the presence of bacterial envelope fraction 1, which is produced most readily at 37°C but not at temperatures below 28°C. Consequently the FA test is best performed on smears of animal tissues, aspirates of exudates such as those from buboes, or cultures incubated at 37°C. This test makes possible the rapid presumptive

identification of *Y. pestis*. Clinical specimens that were frozen or refrigerated after collection are suitable for immediate FA examination because bacterial growth is restricted. If growth has not been inhibited in transit, the specimen should be incubated at 37°C or inoculated into an appropriate laboratory animal to enhance production of envelope antigen fraction 1. Cross-reactions with *Y. pseudotuberculosis* have been recorded, and occasional strains of *Y. pestis* may not stain or may exhibit weak staining. If a positive FA test is supported by epidemiologic and clinical evidence, there is little doubt of the diagnosis.

## EPIDEMIOLOGY

Owing to the great variety of mammalian hosts, fleas, and environmental conditions involved the ecology of plague is complex. The bacilli exist in nature in two broad and not entirely discrete ecologic forms: *enzootic plague* and *epizootic plague*.

Enzootic plague implies a stable rodent-flea infection cycle that is maintained in a relatively resistant host population without excessive host mortality. Enzootic foci serve effectively as long-term reservoirs of infection, but are inconspicuous and difficult to identify.

Epizootic plague occurs when plague bacilli are introduced into rodent or other small mammal populations that are moderately or highly susceptible to the lethal effects of the infection. Because mortality is high, such epizootics are often conspicuous, especially among larger colonial rodents, such as prairie dogs. The risk of exposure is high whenever humans come into contact with epizootic plague—for example, dwelling near ground squirrel populations, hunting, or camping.

Plague foci occur throughout the world. In the United States, *Y. pestis* is permanently established from the eastern slope of the Rocky Mountains westward. Periodic expansion has been detected as far east as the 98th parallel in Texas, the 100th parallel in the midwestern states, and into bordering Mexico and Alberta, Canada. During the first quarter of this century, plague in humans in the United States usually resulted from contact with domestic rats and their fleas. The hazard of rat-borne plague was reduced with the development of rat control programs and the application of higher standards of sanitation in urban areas and on ships. From 1925 to 1960, a yearly average of one case of plague resulted from rural exposures to small, wild mammals or their fleas. An annual average of three cases occurred in the 1960s, eleven in the 1970s, 24 from 1981 to 1985 and 12 from 1986 to 1988. Of all cases since 1945, 87% have occurred in the Rocky Mountain States. Except for one urban case traced to a fox squirrel (*Sciurus niger*) in 1968, cases in the past 55 years have resulted from exposure in rural or suburban settings.

Men predominate both in frequency (58% of cases) and case fatality (19% compared to 12% in women). Half of the cases occur in persons under 20 years of age. The principal sylvatic animals involved have been ground squirrels (*Spermophilus* spp.), prairie dogs (*Cynomys* spp.), chipmunks (*Eutamias* spp.), marmots (*Marmota* spp.), deer mice (*Peromyscus* spp.), and hares (*Lepus* spp.). In the Rocky Mountain states, epizootics among rock squirrels (*Spermophilus variegatus*) are often the ultimate source of infection in humans; following die-off of their customary host, the vector fleas are transported by domestic pets or wood rats nesting in residences. Infection of humans from lagomorphs (rabbits and hares) usually results from tissue contact rather than flea bite, and it occurs predominantly in the fall and winter months. Voles (*Microtus* spp.) and deer mice are reservoirs of enzootic plague in the western United States but have not often been a direct source of plague in humans.

**HISTORICAL PROFILE:** Old Testament references to plague among the Philistines in the eleventh century BC are controversial but, although a certain caution is required, they are not necessarily incorrect. Another outbreak may have occurred in Egypt around 300 BC.

But the confirmed history of plague is split into three pandemics. For plague, and only plague, the term pandemic takes on a modified meaning. It refers not to a single event but to a series of cycles.

***The First Pandemic.*** The disease, possibly originating in East Africa, arrived in Constantinople, capital of the Byzantine Empire, in 541. The death toll of this epidemic, sometimes called the Plague of Justinian after the emperor of the time, was considerable. Plague spread around the Mediterranean, causing a substantial depopulation. A further 16 cycles have been identified, the sequence ending around 760.

***The Second Pandemic.*** The initial wave is known as the Black Death. Originating in one of divisions of the Mongol Empire, possibly because of climatic changes, the disease cut a massive circular swathe of death through Europe, finishing close to where it began. At the same time, a separate arm devastated the Islamic Middle East. China was also severely affected. Plague entered England in 1348, causing most of the estimated 1.5 million deaths in 1349. From 1361 to 1665, 33 cycles of plague are traceable on a national scale. Eastern Europe, often dominated by the numerous phases of the Russo-Turkish War, continued to experience plague to the end of the eighteenth century.

***The Third Pandemic.*** Beginning in south-west China in 1873, the disease reached Canton in 1894 to kill more people than did the Great Plague of London in 1665. A similar toll resulted in Hong Kong. It was here that the bacillus was first identified. From Hong Kong, the disease was transported to India, where an estimated 12.5 million people died of plague between 1897 and 1957. The bacillus spread to Australia, North America, South America, and South Africa. However, partly because of the intervention of modern medicine and preventative measures, the Third Pandemic has had little opportunity to exhibit plague's cyclic nature, though minor outbreaks and cases of the disease continue to be reported in various parts of the world.

*Yersinia pestis* has probably shaped history more than any other micro-organism. No other disease has been able to influence population trends for such long periods. Each pandemic involved a different strain of the bacillus (in turn, *antiqua*, *mediaevalis*, and *orientalis*). Although numerous 'local' theories have been tendered to explain the passing of the Second Pandemic from Europe, it can be argued from a more 'global' standpoint that both this and the First Pandemic were essentially brought to an end by a build up of natural immunity.

### **Incursion in Humans**

Human-to-human transmission of plague may result from pneumonic spread, human flea transmission, or spread by infected exudates. Human flea transmission is uncommon and has not been observed in the United States. Transmission by an infected exudate was noted in Indonesia when a child with classic bubonic plague (inguinal bubo) developed bilateral purulent dacryocystitis. *Yersinia pestis* was recovered from the pharynx of the boy's father, who did not develop an associated illness, presumably because of sulfonamide prophylaxis.

When the flea takes a blood feed from an infected rat, the flea itself often becomes infected. The rat normally dies from plague and the flea seeks another host, so passing on the disease. As rat numbers dwindle, the flea has little choice but to accept an alternative mammalian host - such as man. The human body's response on being injected with plague bacilli by the flea is to filter out the micro-organisms at the nearest lymph node for destruction and disposal. Since the leg is the most frequent site of flea feeding, the lymph node in the

groin is thus the most likely to be affected. Hence the name bubonic plague (Greek *boubon*, groin).

However, in the lymph node the bacilli multiply more rapidly than the body's defence system can overcome them. The intensely painful node ruptures, usually internally. Bacilli enter the blood stream. A feature of *Yersinia pestis* is that it not only produces toxins when active, but if killed, other toxins are released from its casing. Dead or alive, the micro-organism of plague poisons the blood. The toxins spread throughout the body, killing the body's cells. Blood vessels are eaten away, allowing blood to ooze into tissue space. Near the body's surface this process gives rise to characteristic areas of blackened skin. The victim experiences headache, vomiting, giddiness, thirst, pain in the limbs, intolerance to light, sleeplessness, and possibly delirium. The heart pounds faster as blood pressure drops. If the body cannot stop the bacilli then death from shock occurs. The bubonic course generally takes but a week.

Pneumonic plague, the most serious form of plague in humans, has its start from pulmonary involvement following bubonic or septicemic plague. Because *Y. pestis* is not effectively airborne, but rather is transmitted by droplets, the communicability of plague pneumonia is difficult to predict. Contact (droplet) transmission varies with environmental conditions and with the presence and nature of cough in the patients. Cough producing only thick, tenacious material is unlikely to produce tiny droplets (1-5  $\mu$ m) that may be inhaled into the lower respiratory tract. Larger droplets may impinge on the upper respiratory tract, resulting in pharyngeal plague. Primary plague pneumonia occurs primarily in persons in close and prolonged contact with another person with pneumonic plague. Hence, respiratory transmission occurs most frequently to medical personnel or household contacts who are directly involved with the care of the patient.

Plague pneumonia has been rare in the United States, and primary pneumonic plague in contacts has not been detected since 1925. However, from 1975 through 1988, 36 cases of confirmed plague with pneumonia have occurred; 4 appeared to be primary plague pneumonia acquired from domestic pets. During 1980, a 47-year-old woman with primary pneumonic plague had contact with about 180 persons before her 3-day course of illness ended fatally. Plague was diagnosed 4 days after her death. All contacts received abortive therapy ("prophylaxis") although the incubation period for secondary spread to most of the contacts (except household and medical contacts) had been exceeded. Cavitation is an unusual complication of plague pneumonia. Of particular danger if plague pneumonia develops is the possibility of long-distance travel prior to hospitalization.

## **PATHOGENESIS AND PATHOLOGY**

The development of *Y. pestis* in fleas involves the formation of masses of plague bacilli and fibrinoid material in the midgut. If blockage of the proventriculus (foregut) results, the flea cannot successfully ingest a blood meal. A blocked flea tends to desiccate and aggressively makes repeated attempts to feed; at each attempt, being unable to pass the blood meal past the blocked proventriculus, it regurgitates several thousand microorganisms into the site of the bite. Holding infected oriental rat fleas (*Xenopsylla cheopis*) in the laboratory at temperatures over 27°C (80°F) allows clearing of the proventricular blockage; a practical effect of this phenomenon is that plague epidemics have long been observed to subside spontaneously when ambient temperatures remain above 27°C to 30°C (80°F to 85°F).

Once *Y. pestis* is introduced into a human, a progressive infection generally results unless specific antimicrobial therapy is given. Nearly every organ and tissue of the body may be involved, with the production of acute or indolent signs and symptoms referable to a wide variety of organ systems. Depending on the length of survival, pyogenic, necrotic, infarctive, inflammatory, hemorrhagic, and edematous lesions are found in many tissues and organs, particularly the regional lymphatics, spleen, liver, lungs, skin, and mucous membranes. There may be circulatory collapse, a bleeding diathesis, and peripheral thrombotic phenomena resembling the reactions associated with the endotoxins of other gram-negative microorganisms. Suboptimal antibacterial therapy favors the development of complications and possibly the establishment of resistant bacteria. Progressive circulatory failure may develop in severe infections, and sudden death from cardiac failure has occurred, even in convalescence.

On introduction into a human, flea-borne *Y. pestis* is susceptible to phagocytosis and destruction by polymorphonuclear leukocytes. However, plague bacilli engulfed by mononuclear phagocytes may become resistant and may give rise to septicemia, either after regional lymph nodes are involved (bubonic plague) or without apparent lymphadenopathy (primary septicemic plague). Primary pneumonic plague is fulminant, resulting in severe prostration, respiratory distress, and death within 1 to 3 days. The primary involvement of a vital organ (e.g., the lungs) by direct inoculation with plague bacilli that are phagocyte-resistant from the outset—as is the case with *Y. pestis* from a mammalian source—probably contributes to the fulminant course of pneumonic plague.

## MANIFESTATIONS

The incubation period in bubonic plague is generally 2 to 6 days; in primary pulmonary plague it is 1 to 3 days. The severity at onset is variable. In the less malignant form, the initial manifestations are general malaise, fever, and pain or tenderness in an area of regional lymph nodes; there may be enlargement of the involved lymph nodes—buboes. Most often present in the inguinal or axillary regions, buboes may occur anywhere and in the past decade have been noted in supraclavicular, epitrochlear, cervical, post-auricular, facial, subpectoral, and popliteal regions. At this stage of the disease, toxicity may be minimal, but intermittent bacteremia occurs in most patients, as shown by the isolation of *Y. pestis* from at least one of a series of blood cultures. In more severe infections, or when treatment is delayed, the disease progresses rapidly to a septicemic phase: all blood cultures are positive for *Y. pestis* (ideally three or more), with the classic findings of toxicity, prostration, shock, and occasionally, hemorrhagic phenomena. The progression of infection can be extremely rapid—a patient appearing to be mildly ill, with complaints limited to fever and adenitis, may become moribund within hours.

In some patients, the onset of symptoms may be quite striking, with high, remittent fevers, chills, myalgias, headache, and severe malaise. Occasionally, buboes cannot be detected for several days after the onset of symptoms. Lack of early adenitis makes diagnosis difficult; clinical findings are not specific, and the clinician is not likely to consider obtaining a lymph node aspirate unless tenderness directs attention to a possible lymphadenitis. If bacteremia is present, the plague bacilli may sometimes be observed in a smear of peripheral blood—a grave prognostic sign. Less common symptoms include abdominal pain, nausea, vomiting, constipation followed by diarrhea (frequently bloody), skin mottling, petechiae, and circulatory collapse. Rarely, vesicular and pustular skin lesions occur. The gravity of the illness is indicated by varying degrees of restlessness, apathy, anxiety, apprehension, seizures, and coma.

Plague pneumonia is not clinically unique and is often complicated or mimicked by adult respiratory distress syndrome (ARDS); cavitation is uncommon, usually consisting of small lesions that resolve quickly without roentgenographic evidence of residua.

## DIAGNOSIS

The classic feature of plague contracted by cutaneous inoculation is an excruciatingly painful bubo. This finding in a patient with fever, prostration, and a history of possible exposure to rodents, rabbits, or fleas in the western United States should lead to the inclusion of plague in the differential diagnosis. Tularemia may mimic this clinical and epidemiologic picture; however therapy is the same for both diseases. In recent years bubonic plague has been diagnosed in cases ultimately found to have been adenitis caused by *Francisella tularensis*, *Streptococcus* spp, or *Staphylococcus aureus*; conversely, tularemia has often been diagnosed in cases subsequently confirmed as bubonic plague. Sporadic cases of primary septicemic plague are particularly difficult to recognize because there are no specific findings. Other comparably severe infectious diseases that may be confused with septicemic plague include meningococemia, sepsis caused by enteric gram-negative bacteria, and certain rickettsioses. Inguinal hernia and acute appendicitis-especially if there is severe intra abdominal lymphadenopathy-may have to be considered. Careful evaluation of pulmonary involvement may help to differentiate ARDS from plague pneumonia, but usually public health decisions must be made before the diagnosis is established. As soon as a diagnosis of suspected plague is made, local and state health officials must be notified so that epidemiologic investigation and control measures can be instituted. At least four blood cultures should be obtained; these may be taken within 1 hour and should not delay initiation of specific therapy. Blood, bubo, and parabubo aspirates, exudates, purulent drainage, and sputum should be examined by microscopy (smears stained with dyes and fluorescent antibody), culture (liquid and agar), and animal inoculation. Giemsa's or Wayson's methods of staining smears are particularly valuable for rapid, tentative diagnosis because bacteria morphologically consistent with *Y. pestis* are frequently demonstrable. Gram-stained preparations are less helpful because the characteristic bipolarity may not be readily discernible.

Buboes and abscesses should not be excised, or incised and drained, for diagnostic purposes. However, careful needle aspiration of an involved lymph node is essential to determine the microbial etiology of the lymphadenitis. The value of this procedure far exceeds the risk associated with judicious manipulation. The procedure should not be done until after blood cultures have been obtained; therapy may be started either concurrently with the aspiration or immediately after microscopic examination of stained smears of the aspirate. In the face of negative smear examination, therapy may need to include drugs effective against gram-positive and gram-negative causes of lymphadenitis (including plague when the suspicion is reasonably well based). Most bacteria with the exception of *Y. pestis*, other *Yersinia* spp, and *F. tularensis*, should grow readily within 24 hours. Negative cultures of aspirates at 24 hours should sharply increase the suspicion that plague or tularemia is the correct diagnosis. Acute and convalescent serums should be obtained from all patients suspected of having plague to enable an etiologic diagnosis in the event microorganisms cannot be isolated.

The several diagnostic efforts described permit cases of plague to be categorized as (1) *suspected* plague-appropriate clinical and epidemiologic findings or demonstration in stained smears of bacteria consistent with *Y. pestis*; (2) *presumptive* plague-FA-positive clinical specimens or a single, elevated antibody titer in an unvaccinated person with a plaguelike illness; (3) *confirmed* plague-isolation of *Y. pestis* from clinical materials or a fourfold rise or

fall in specific antibody. Only presumptive and confirmed plague cases are officially reported in the United States, because appropriate laboratory studies are readily available to confirm infection with *Y. pestis*. However, if the diagnosis of suspect plague is strongly supported by appropriate epidemiologic, ecologic, and clinical evidence, the case may be accepted for official reporting by the Plague Branch of the Centers for Disease Control (CDC).

## **PROGNOSIS**

Without treatment, the case-fatality ratio in bubonic plague is about 60%; in septicemic and pneumonic plague it is probably 100%. With early therapy, the mortality in bubonic plague should approach zero; however, the fatality rate of reported cases since 1975 has been 16%. The prognosis is poor in primary pneumonic plague if therapy is delayed more than 18 hours after the onset of symptoms. Age and general physical condition also affect survival in septicemic and pneumonic plague.

The immediate, life-threatening complications of plague are shock, hyperpyrexia, convulsions, and disseminated intravascular coagulation (DIC). In addition, hematogenous or lymphogenous dissemination may occur early in the disease. Antibacterial therapy that is inadequate or inappropriate (e.g., use of ampicillin) appears to favor the development of metastatic infections such as plague meningitis, secondary pneumonia, endophthalmitis, and multiple lymph node involvement including intraabdominal and perihilar nodes.

Primary buboes may resolve slowly, despite appropriate chemotherapy, with pain and tenderness persisting for weeks.

Patients who have been severely ill should be observed for evidence of progressive cardiac failure, a rare but critical complication that may not occur until late in the recovery phase. The cardiac-active glycosides are effective.

In patients who survive severe septic shock, marked necrosis of peripheral tissues may occur. Nursing care is vital to limit the amount of damage. Devices that further limit already compromised peripheral circulation to fingers and toes (e.g., arm boards or other restraints) should be applied cautiously or not at all.

Prior to the availability of specific antimicrobial therapy, plague during pregnancy often resulted in abortion, although *Y. pestis* was not regularly present in the fetal tissues. With early therapy in the mother, the pregnancy should not be adversely affected. In cases in which delivery occurs within 48 hours after therapy is initiated in the mother, the newborn should be considered exposed to *Y. pestis* either by the transplacental route or (more likely) by contact with the mother's blood during delivery and should be treated.

## **THERAPY**

Because secondary plague pneumonia may already have developed, all patients with bubonic plague should be strictly isolated until 48 hours after specific therapy has been instituted. Isolation may be discontinued if respiratory symptoms or purulent drainage does not develop. Exudates or purulent discharges should be handled with rubber gloves. Facemasks, including eye protection, are indispensable in caring for patients with pulmonary plague.

Nonspecific therapy consists of symptomatic and supportive management of complications such as shock, high fever, and convulsions. Fluid needs may require intravenous supplementation. Glucocorticoids (e.g., methylprednisolone, 30 mg/kg body wt/day by IV injection as a single dose for 2-3 days) should be considered in management of life-threatening toxemia and shock after specific antimicrobial therapy is instituted. Diazepam is beneficial in reducing apprehension and restlessness.

Antimicrobial therapy should be started promptly, without waiting for laboratory confirmation, after specimens have been obtained for diagnosis. The most effective drug against *Y. pestis* is streptomycin. Other effective drugs include kanamycin, chloramphenicol, the tetracyclines, and certain sulfonamides (e.g., sulfadiazine). The penicillins are not effective in treating plague, although these drugs frequently show activity in vitro; ampicillin was suboptimal in experimental murine plague, and may have been life-sparing in humans treated with it before the correct diagnosis was suspected. Gentamicin has been successful in treating plague in humans and in experimental murine plague. Because of greater experience, it is still preferable to use streptomycin. Studies have not been done to determine the effectiveness of doxycycline in treating plague.

Because streptomycin is rapidly lethal to *Y. pestis*, it must be given circumspectly in the hope of avoiding a rapid and massive release of plague endotoxin, for example, 30 mg/kg body wt/day by IM injection of four equal portions, 6 hourly, for up to 10 days. If clinical considerations (e.g., potential for hearing loss in the elderly and patients with impaired renal function) predicate a shorter course, streptomycin may be given for 5 days. Ten days or more of total antibacterial therapy may be accomplished by overlapping an alternative to streptomycin for at least 24 hours before the streptomycin is stopped.

Tetracycline and chloramphenicol have been effective when used alone, but in patients who have pneumonia or are severely ill with plague, streptomycin is the preferred antimicrobial. The sulfonamides cannot be recommended when more effective and safer alternatives are available.

If there is meningitis or endophthalmitis, chloramphenicol should always be included in the regimen of therapy because of its relatively unrestricted entry into these areas.

During pregnancy, streptomycin or gentamicin should be used unless chloramphenicol is specifically indicated as noted above.

Newborns delivered during the potentially bacteremic phase of maternal plague should be treated either with kanamycin (15 mg/kg body wt/day injected IV or IM as four equal portions, 6-hourly) or streptomycin (10-20 mg/kg body wt/day injected IM as four equal portions, 6-hourly). Tetracycline (30 mg/kg body wt/day perorally as four equal portions, 6-hourly) and chloramphenicol (15-25 mg/kg body wt/day perorally as four equal portions, 6-hourly) are both potentially hazardous alternatives.

All contacts of patients with pulmonary involvement, whether primary or secondary, should be quarantined and given either tetracycline (30 mg/kg body wt/day perorally as four equal portions, 6-hourly) or trisulfapyrimidines (60-75 mg/kg body wt/day perorally as four equal portions, 6-hourly for 10 days). Other effective drugs that may be used for prophylaxis of contacts include chloramphenicol or sulfadiazine.

Chemoprophylaxis is not routinely indicated for household and community associates of patients with bubonic plague. Community and regional residents should be kept under surveillance for the detection of additional cases. Field studies must be undertaken to define and control the source of cases in humans.

## **PREVENTION**

A heat-killed vaccine prepared from *Y. pestis* produces humoral antibody in over 90% of recipients after administration as a primary series of three injections with the second and third doses given 4 and 16 weeks after the first dose. Booster injections are recommended every 6 months to maintain immunity. After a total of five doses of vaccine have been given, booster doses may then be given empirically at annual or biennial intervals, or preferably, when the passive hemagglutination antibody to fraction 1 of *Y. pestis* falls below 1:128.

Severe inflammatory reactions localized to the site of injection are frequent, and systemic reaction to the vaccine occurs occasionally. Active immunization is recommended only for persons at high risk—those engaged in military or other field operations and activities that must be carried out in areas endemic for plague or those in situations in which exposure to rodents and fleas cannot be controlled. Trained personnel using proper equipment in clinical laboratories or conducting plague investigations in field or laboratory fall into the high-risk group if they handle strains of *Y. pestis* that are resistant to antimicrobial agents or if aerosols of plague bacilli are produced. The general adequacy of standard bacteriologic procedures is attested by the fact that only four instances of laboratory plague infection in the United States have been reported since 1900.

Field exposures have resulted in human infections when sick or dead animals have been skinned and examined without appropriate precautions. Both infestations by the animals' ectoparasites and direct contact with tissues must be avoided.

The primary preventive or suppressive measures against urban plague consist of rigorous environmental sanitation aimed at reducing or eliminating commensal rodent populations, particularly rats and their fleas. In areas where enzootics or epizootics of plague are in progress, steps to reduce the host rodent population should be delayed until they can be undertaken concurrently with, or after, an effective flea control program. Rodent reduction alone would result in a massive release of infected fleas, increasing the potential for human exposure and further epizootic spread. In countries or areas where standards of sanitation are high and commensal rodents are few, plague should be uncommon. However, as long as plague continues to exist anywhere in the world, uncontrolled domestic rat populations are a hazard wherever they exist.

# LEISHMANIASIS

Leishmaniasis is a group of diseases caused by protozoa of the genus *Leishmania* that are normally parasites of canines and rodents. They only infect humans under certain circumstances, mainly as zoonoses. Transmission is effected by sandflies of the genus *Phlebotomus* in the Old World and *Lutzomyia* in the New World.

## ETIOLOGY

The leishmanias that cause leishmaniasis in humans are divided into two subgenera: *Leishmania leishmania* spp. and *Leishmunia viannia* spp. A general infection of the reticuloendothelial system, visceral leishmaniasis or kala azar, is caused by *L. leishmania infantum*, *L. leishmania donovani*, and *L. leishmania chagasi*. Purely cutaneous disease, cutaneous leishmaniasis of the Old World or oriental sore, is caused by *L. leishmania major*, *L. leishmania tropica*, and *L. leishmania aethiopica*. New World cutaneous leishmaniasis, also a purely cutaneous disease, is caused by *L. leishmania mexicana* and *L. leishmania amazonensis*. Of the *L. viannia* spp., *L. viannia braziliensis*, *L. vianniaguyanensis*, and *L. viannia panamensis* cause cutaneous and mucosal disease-mucosal leishmaniasis, espundia, or pian bois; *L. viannia peruviana* causes the purely cutaneous disease, uta. These species are morphologically identical but may be differentiated by cultural and biochemical methods. Also, their clinical manifestations and epidemiology are strikingly different.

## EPIDEMIOLOGY

Leishmaniasis is essentially a zoonosis and may be found in an environment that varies from the humid rain forests of South and Central America to the dry savannahs of Africa south of the Sahara and the deserts of the Middle East. The actual reservoirs vary correspondingly, although transmission of leishmanias to humans occurs primarily by way of sand-flies (excepting the rare instances of transmission of *Leishmania donovani* by blood transfusion and the alleged coital transfer of the same parasite).

Sandflies are infected as they feed on mammals with leishmaniasis. The ingested amastigotes develop into promastigotes, the infective forms, in the anterior portion of the gut, and these move to the salivary glands in about 10 days. Inoculation of a susceptible mammal can then occur as the sandfly feeds.

Considerable moisture is needed to induce oviposition in the sandfly, and breeding places vary in different parts of the world. A humid microclimate with decomposing organic matter is usually needed. The life cycle of the sandfly lasts from 1.5 to 2 months in the summer but is extended in the winter months. Adults are normally nocturnal, but some sandflies bite during the day. Flight ranges vary from a few to hundreds of yards.

### Visceral Leishmaniasis (Kala Azar)

The clinical syndrome of visceral leishmaniasis (VL), or kala azar, is commonly caused by *L. leishmania infantum*, *L. leishmania donovani*, and *L. leishmania chagasi*. However, the epidemiology of these species differs.

**Leishmania leishmania infantum.** The reservoir hosts of *L. leishmania infantum*-dogs, foxes, and jackals-are found in the Mediterranean, Middle East, and Central Asian regions, as well as the Sudan and China.

**Mediterranean.** In North Africa and the nearby Mediterranean islands, the dog is the most important host. The disease is urban and sporadic, occurs mainly in infants (*Ponos*-infantile kala azar), and shows a seasonal pattern, appearing from April to October with

infection having taken place in the previous fall. Following the eradication of malaria, kala azar became uncommon; however, in southern Europe, there has been resurgence. The zoonotic host is the European fox (*Vulpes vulpes*); accordingly, the disease in this area is rural and sporadic, but there have been small epidemics in Italy where the majority of the infections were subclinical.

**Middle East.** Kala azar is found sporadically in Iran, Saudi Arabia, Oman, Yemen, and Aden. However, it has become almost epidemic on the outskirts of Baghdad, where jackals are probably the zoonotic host.

**Central Asia.** Kala azar is now confined to Azerbaijan and an area in Tadjikistan where jackals are the zoonotic host.

**Sudan and Sub-Saharan Africa.** In the Sudan, rodents infected with *L. leishmania infantum* have been found and are possible primary hosts. This is the only area where infected rodents have been found.

**China.** The disease is still present in China, with *L. leishmania infantum* in the West, and *L. leishmania donovani* in the East. As well as the dog, the raccoon dog is a host.

**Leishmania leishmania donovani.** Solely a parasite of humans, *L. leishmania donovani* causes both endemic and epidemic disease in India and East Africa. The reservoir in humans includes both those with subclinical infections and those with postkala azar dermal leishmanoid (PKDE); the skin lesions of PKDE contain viable protozoa that persist for many years.

In India, epidemics of donovonian visceral leishmaniasis have now returned because of an increase in the peridomestic sandfly (*Phlebotomus argentipes*) following the cessation of efforts to eradicate malaria. Major epidemics have occurred in East Africa, where the vector, *Phlebotomus martini*, lives in eroded termite hills situated close to homesteads. The disease is also found in Eastern China.

**Leishmania leishmania chagasi.** Sporadic zoonoses caused by *L. leishmania chagasi* occur in Central and Northern South America. In Brazil the disease is common in the dry northeast, where the dog is the reservoir in urban areas and the fox in rural areas. Foxes are also reservoirs near the Amazon. Most of those infected are between 4 and 14 years of age.

### **Old World Cutaneous Leishmaniasis (Oriental Sore)**

**Leishmania leishmania major.** Zoonotic cutaneous leishmaniasis (XL), the common form of Old World cutaneous leishmaniasis, is usually caused by *L. leishmania major*. In endemic areas, it is largely a disease of children because most adults are immune; however, visitors and immigrants to new agricultural projects may be infected.

**Leishmania leishmania tropica.** Anthroponotic cutaneous leishmaniasis (ACL) is caused by *L. leishmania tropica*. Although the disease has largely disappeared from Southern Europe and the cities of the Middle East, it is common in Afghanistan. Humans are the main reservoir, but dogs may be secondarily infected.

**Leishmania leishmania aethiopica.** In the mountainous regions of Ethiopia and East Africa where hyraxes are the reservoir hosts, there is a high incidence of diffuse, cutaneous leishmaniasis caused by *L. leishmania aethiopica*.

### **New World Cutaneous Leishmaniasis**

**Leishmania leishmania mexicana.** Chiclero's ulcer is caused by *L. leishmania mexicana*. It is found in Central America as far south as Panama and is the only form of cutaneous leishmaniasis in Mexico and Guatemala. Relatively small enzootic foci are perpetuated in the humid rain forest areas of the Peten region of Guatemala and the Yucatan area of Mexico by *Lutzomyia flaviscutellata*, which feeds mainly on rodents. Transmission to

humans is effected by anthropophilic species such as *Lutzomyia panamensis*. Humans are infected when they enter the forest to cut wood or collect gum (chicle). Thus, the disease has been called chicle ulcer.

**Leishmania leishmania amazonensis.** In the northern and central parts of South America, *L. leishmania amazonensis* infects forest rodents. In the rare cases of human infection, diffuse cutaneous leishmaniasis is the usual form.

**Leishmania viannia braziliensis.** The Amazon region as far south as northern Argentina is the range of *L. viannia braziliensis*. Espundia is a severe, disfiguring, potentially fatal mucocutaneous disease of the forest; it has seriously retarded development of the Amazon region where it has halted building the trans-Amazon highway and driven out settlers on newly cleared forest land.

**Leishmania viarmia panamensis.** Found in Central America, *L. viannia panamensis* does not cause serious disease.

**Leishmania vianuia guyanensis.** In the northeastern coastal regions of Guyana and Surinam, *L. viannia guyanensis* causes pian bois (forest yaws), a nonmucosal disease with extensive lesions, in persons living in newly constructed suburbs of towns on the edge of the forest.

**Leishmania viannia peruviana.** Occurring in the valleys of the Western Andes, *L. vianniu peruviana* almost disappeared following spraying with DDT. It has returned, but does not cause serious disease. Dogs are thought to be the reservoir hosts.

**Leishmania viannia garnhami.** Found in the rain forest of the Eastern Andes in Venezuela, *L. viannia garnhami* does not cause severe disease. Dogs are the reservoir host.

## MANIFESTATIONS

### Inapparent Infection

Not all persons infected with leishmanias develop disease. In fact, the number infected is probably far larger than the number diseased. Leishmanin skin testing in areas endemic for leishmaniasis has shown a high incidence of positive reactors; the percentage increases with increasing age. Conversion to positive may take place without such indications of overt infection as a history of skin ulcers, presence of scars, or kala azar. Furthermore, in an area where kala azar appeared for the first time, it was shown that leishmanin conversion, humoral antibodies, and hepatic granulomas had developed without any illness.

### Visceral Leishmaniasis (Kala Azar)

All the geographic forms of kala azar are generally similar in their clinical manifestations. A primary skin lesion occurs in the African form, and amastigotes are found in the skin in the African, American, and Chinese forms. Post-kala azar dermal leishmanoid is common in the Indian, less common in the African, and very rare in all the other forms.

The primary lesion at the site of the infective bite is usually so small that it cannot be distinguished. In the Sudan, more extensive lesions resembling epitheliomas have been described.

Infection without manifestations persists for 4 to 6 months, and can persist for up to 10 years. When the protozoa invade the reticuloendothelial cells of the spleen, liver, bone marrow, and lymph nodes, disease is provoked.

The onset of symptoms may be abrupt or, as is common in the inhabitants of endemic areas, more insidious. Patients often have a cough, and an attack of pneumonia may cause the patient to be admitted to the hospital. Diarrhea, even dysentery, and epistaxis with fever are also common. An insidious onset is marked by chronic, wasting disease. The patient typically experiences pain beneath the left costal margin from an enlarging spleen.

In cases with an acute onset, the fever starts suddenly and may reach 104°F. Rarely, there is a characteristic pattern with two maxima during the day. In the more chronic cases, there is little or no fever. Typically, there is marked fever with little constitutional illness so that the patient is ambulant.

The inguinal and femoral lymph nodes usually are moderately enlarged, and enlargement is especially notable in the African form. The spleen enlarges gradually and may eventually reach into the right iliac fossa. At first it is soft, but it soon becomes very hard. The liver also enlarges, but not as markedly. Jaundice occurs in the 10% of patients who are most severely ill.

The concentration of IgG in the serum may rise as high as 4 g/dl. A positive formol gel reaction is usual. Proteinuria is present in some patients, to a degree that is more marked than can be accounted for by the fever. A normocytic, normochromic anemia is marked. Pancytopenia develops and progresses, partly as a result of an autoimmune phenomenon in which antibody attacks and destroys the formed elements of the blood, but mainly as a consequence of hypersplenism. The halflife of erythrocytes is greatly reduced because they are destroyed by the spleen and other parts of the reticuloendothelial system; splenectomy is salutary.

### **Old World Cutaneous Leishmaniasis (Oriental Sore)**

Two different forms of cutaneous disease are caused by *L. leishmania major* and *L. leishmania tropica*: (1) rural or zoonotic cutaneous leishmaniasis (ZCL) is caused by *L. leishmania major* and is characterized by a short incubation period, rapid initial growth of the amastigotes, even with spread to regional nodes, considerable tissue reaction in the multiple lesions, eventuating in few amastigotes with healing in less than 1 year and (2) urban or anthroponotic cutaneous leishmaniasis (ACL) is caused by *L. leishmania tropica* and is characterized by a longer incubation period, slower growth of the amastigotes, less pronounced tissue reaction in the usual single lesion that contains more amastigotes but healing in more than 1 year

The incubation period is variable from days, weeks, or months, and it can last as long as 3 years.

The local lesion begins as a minute, itching papule that tends to expand as shotty, congested infiltration of the dermis. After a few days or weeks, the papule becomes covered with fine papery scales that later become moister, browner, and adherent. In this way, a crust is formed; when the crust falls off or is scratched, a shallow ulcer is uncovered. The sore, which is surrounded by an area of congestion, slowly extends by erosion of its edge. Subsidiary sores arise around the edge of the ulcer and merge with it. These sores are usually about 2 cm in diameter, and they may enlarge to occupy an area several cm across. After 2 to 12 months or more, healing sets in, often beginning at the center while the ulcer may be extending at the edge. Ultimately, a depressed white or pinkish scar forms.

### **American Leishmaniasis**

Two very different kinds of cutaneous leishmaniasis occur in Central and South America: (1) single, non-metastasizing lesions that heal spontaneously after a few months, caused by *L. leishmania mexicana* and *amazonensis*; and (2) multiple lesions, sometimes with mucosal spread (espundia) or lymphatic spread (Pian bois, forest yaws) that may persist and even be lethal, caused by *L. viannia braziliensis* and *guyanensis*.

**Chiclero's Ulcer (Bay Sore).** Caused by *L. Leishmania mexicana*, the typical lesion is found on exposed areas of the body, usually the face, commonly on the ear, where it causes a chronic ulcer that persists as long as 20 years and causes destruction of the pinna Elsewhere, the lesion is small and self-limiting, healing spontaneously in less than 6 months.

**Diffuse Cutaneous Leishmaniasis.** A single, self-healing sore is the usual outcome of infection with *L. leishmania amazonensis*. In about 30% of cases, however, severe, disfiguring cutaneous disease results.

**Espundia.** Disease caused by *L. viannia braziliensis* begins as an ulcer on an exposed area of the skin or mucous membranes. It heals in a few months to years, leaving a characteristic scar.

## DIAGNOSIS

The diagnosis of leishmaniasis is reliably made by the demonstration of the protozoa in smears and by isolation either in cultures or by animal inoculation. In cutaneous or mucocutaneous leishmaniasis, a specimen for examination is obtained by inserting a small needle under the ulcer, going through the skin peripheral to the lesion. In this way, relatively uncontaminated tissue juice can be obtained for the preparation of smears (staining by Giemsa's method), cultures (NNN medium or Schneider's insect medium), or inoculation (hamsters). Amastigotes are abundant in Old World cutaneous leishmaniasis but are scanty in the New World form.

It is important in American leishmaniasis to distinguish between the two subgenera. *Leishmania leishmania* spp. cause only cutaneous lesions whereas *Leishmania viannia* spp. cause both mucosal and cutaneous lesions. *Leishmania leishmania* spp. grow rapidly in culture and produce skin lesions in hamsters readily, whereas *Leishmania viannia* spp. grow slowly or not at all in culture and produce skin lesions in hamsters only with difficulty.

A full-thickness biopsy of the skin through the edge of a lesion may be especially useful in the diagnosis of Old and New World leishmaniasis.

In kala azar, specimens for examination, in descending order of usefulness, are spleen pulp, sternal marrow, liver tissue, and juice from lymph nodes. If the spleen is reasonably large and firm and the prothrombin time is normal, splenic puncture is a safe procedure.

Splenic puncture is positive to a greater extent than any other method of diagnosis. Sternal puncture is safer in some hands, but it is not as often productive. Liver biopsy is also useful. Lymph node puncture is positive only in about 60% of cases.

The leishmanin skin test is used in the diagnosis of some forms of leishmaniasis. Leishmanin is a suspension of promastigotes obtained from cultures and suspended in 0.5% phenol in saline solution to a concentration of  $10^7/\mu\text{l}$ . Some preparations now are standardized on the basis of nitrogen content. A dose of 0.1 ml to 0.2 ml is injected intradermally. A positive reaction is an area of induration greater than 5 mm in diameter 24 to 48 hours after injection. The reaction becomes positive in the first 6 weeks of infection with *L. leishmania mexicana*, *major*, and *tropica* and after 3 months with *L. viannia braziliensis*; it remains positive for life after recovery. It is of no use in the diagnosis of active disease caused by *L. leishmania donovani*, for it is negative until after recovery. Cross-reactions occur with certain forms of skin tuberculosis but they are rare.

Complement-fixing (CF) antibodies appear in the blood only in kala azar. They appear early and are present while the disease is active, disappearing with cure. The antigen is prepared from an acid-fast bacillus (Kedrowsky's bacillus); titers of 1: 20 or higher are significant. Cross-reactions occur with Chagas' disease and other forms of trypanosomiasis. There are no cross-reactions with tuberculosis or leprosy.

Visceral leishmaniasis must be differentiated from other prolonged fevers of the tropics-malaria, typhoid, liver abscess, brucellosis, disseminated histoplasmosis, and reticulosis. Furthermore, the wasting may resemble that of starvation, pulmonary tuberculosis, malignant disease, or AIDS. The diagnosis is made by isolating amastigotes from spleen, bone marrow, liver, or lymph node aspirates. The formol gel, complement-fixing, and fluorescent antibody (FA) tests are also useful. The splenomegaly must be distinguished from

portal hypertension, schistosomiasis, myelogenous and lymphatic leukemias, and other severe anemias associated with splenomegaly.

## **THERAPY**

Most of the simple cutaneous leishmanial lesions require no chemotherapy because they are self-healing. However patients with mucosal and visceral leishmaniasis must be given specific therapy, as must simple cutaneous lesions from which *L. viannia* spp. have been isolated. Sodium stibogluconate (Pentostam, Solustibosan), or meglumine antimoniate are the agents of choice. In kala azar, resistance to antimony may develop unless adequate doses are given for a long enough period: for example, 10 mg/kg body wt/day, by IM or slow IV injection, for at least 30 days. The clearance of amastigotes from the spleen should be monitored, and if they are still present at 30 days, the dose should be doubled to 20 mg/kg body wt/day, injected IM or IV as two equal portions, 12-hourly, and continued for up to 90 days if necessary. Mucocutaneous leishmaniasis (espundia) should be treated the same way.

Urea stibamine is given by IV injection of 3 mg/kg body wt/day for 30 days. It is of no use in mucosal leishmaniasis.

Pentamidine isethionate is the only drug of value in the treatment of diffuse cutaneous leishmaniasis and pian bois; it is of little use in visceral leishmaniasis. The dose is 2-4 mg/kg body wt, weekly (or at most thrice weekly), by slow IV injection for as long as it takes to effect a cure. Hyperglycemia and diabetes mellitus are serious adverse reactions.

If treatment is effective, small spleens become impalpable within a month; large spleens take several months to diminish in size. The spleen and bone marrow must be free of amastigotes on two occasions separated by 1 week. In visceral leishmaniasis, the concentrations of immunoglobulins revert to normal within 6 months; serologic reactions in both visceral and mucosal leishmaniasis also fall to low titers within 6 months. Short-term relapses occur in visceral leishmaniasis within 6 months and long-term relapses may occur up to 2 years after treatment. Post-kala azar dermal leishmanoid may appear up to 20 years or more after an attack of visceral leishmaniasis. Splenectomy may be of value, and even be curative, in resistant visceral leishmaniasis. However, the disadvantages of splenectomy in the tropics are very great.

## **PREVENTION**

Cutaneous leishmaniasis has been successfully controlled in southern Russia by destroying the wild rodent reservoir. Gerbil colonies were destroyed in their burrows with picrotoxin, and the burrows were covered up. Villages were sited more than 3 miles from any colonies.

In India, where humans are the only known reservoir, mass diagnosis and treatment of all cases of kala azar achieved a fair degree of control before the appearance and use of residual insecticides enabled control of the vector.

Where the sandfly vectors live in close contact with humans, residual spraying with DDT has destroyed the sandflies and stopped transmission. The incursions of Indian kala azar and urban cutaneous leishmaniasis in the Middle East were halted in this way. However, with the cessation of residual spraying for malaria eradication in these areas, sandflies have returned and the transmission of leishmaniasis has resumed, especially in the Middle East. Residual spraying at 6-month intervals is necessary to stop transmission permanently.

Inoculation with living promastigotes of *L. leishmania major* to prevent later infection is practiced extensively with great success in the Middle East. A small lesion is produced on a covered area of the body. Evolution, without chemotherapy, that continues until healing

occurs confers immunity that is apparently lifelong. Successful vaccination against American cutaneous leishmaniasis and kala azar has not yet been achieved.

Leishmanin skin testing is valuable for surveillance. Skin testing of a population on an age basis shows the past and present incidence of infection. Testing can also be used to delineate foci of transmission as well as nonimmune populations that might suffer severely from the infection.

## CUTANEOUS FILARIASIS AND DRACONTIASIS

Juvenile or adult filariae of several species may parasitize the skin and subcutaneous tissues. Three species are primarily pathogens of humans: *Onchocerca volvulus*, the agent of onchocerciasis (river blindness); *Loa loa*, the human eyeworm; and the *Mansonella* species *ozzardi* and *streptocerca*. Some filariae that are primarily parasites of nonhuman animals, principally species belonging to the genus *Dirofilaria*, often infect humans by accident. *Dracunculus medinensis*, the Guinea worm, produces the disease dracontiasis; it is often grouped with the filariae but is, in fact, a very different parasite.

### **Onchocerciasis (River Blindness)**

Infection with *O. volvulus* is manifested by a variety of acute and chronic skin lesions, subcutaneous nodules (onchocercomata), ocular disease and blindness, and lymphadenopathy.

### **ETIOLOGY**

The adult worms typically are enmeshed in fibrous nodules in the subcutaneous tissues, usually over sites where bones are superficial, such as the scalp, ribcage, trochanters, iliac crest, and sacrum. Rarely, the worms may be found free in loose connective tissues of the pelvis or in deeply situated nodules that cannot be palpated. The microfilariae produced by female worms are found widely disseminated in the dermal layers of the skin. The black fly, *Simulium*, is the vector of onchocerciasis. Female black flies ingest microfilariae from the skin in the course of taking a blood meal from an infected human. Microfilariae develop to the infective stage in the fly over a period of 5 to 7 days, depending on ambient temperature. At a subsequent feeding, the infective larvae escape from the fly, are deposited on the skin, and then may invade the tissues at the site of the bite. Once in the human, the infective larvae require about 1 year to become adults, mate, and produce microfilariae. The microfilariae may live as long as 2.5 years; adult worms survive for 7 to 15 years.

### **EPIDEMIOLOGY**

Onchocerciasis is an important medical and public health problem in regions in which it is endemic. In Central Africa, endemic foci are distributed from west to east. In the Western Hemisphere, onchocerciasis is found in Mexico, Guatemala, Ecuador, Colombia, eastern Venezuela and northern Brazil. There is a small focus of infection in Yemen. New foci of infection continue to be reported from various parts of the world.

The marked differences in the patterns of onchocerciasis in different parts of the world are largely attributable to differences in strains of *O. volvulus*. Foci of disease are associated with fast-moving streams and rivers where black flies breed. The biting habits of the vector

species are believed to have considerable influence on the patterns of disease. For example, in areas where the *Simulium* vectors tend to feed on the upper portions of the body, there is a tendency for nodules to be concentrated on the head with microfilarial invasion of the ocular tissues. Where vectors feed on the lower parts of the body, the nodules tend to occur on the lower part of the body and lesions of the eyes are less common. Geographical variations in disease patterns are well known.

## **PATHOGENESIS AND PATHOLOGY**

Typically, adult worms become encapsulated and enmeshed in dense fibrous connective tissue under the skin. Nodules vary greatly in size, from one to several centimeters in diameter, and are most easily detected over bony prominences such as the iliac crest, ends of the long bones, and the head.

## **MANIFESTATIONS**

Itching of the skin is the commonest clinical manifestation of onchocerciasis. The dissemination of microfilariae through the dermis of the skin causes a broad spectrum of acute and chronic skin lesions. There may be transient papular eruptions, hyper- and hypopigmentation, atrophy and hypertrophy of the skin. The migration of microfilariae into the tissues of the eye, particularly into the cornea, with death of the worms, produces lesions that lead to impairment of vision and ultimately to blindness. Lymphadenopathy is commonly associated with onchocerciasis.

## **DIAGNOSIS**

The demonstration of microfilariae in the dermal layers of the skin of the patient is diagnostic. Snips of skin uncontaminated with capillary blood are obtained using a corneal-scleral punch; they are placed in a drop of water or saline, teased to facilitate escape of the microfilariae from the tissues, and examined after 30 minutes or longer for the presence of microfilariae. If teased tissues are allowed to dry on a slide, they may be stained subsequently if detailed study is required. Skin snips may also be taken using a needle to raise the skin and a razor or scalpel blade to cut the snip. The unsheathed microfilariae have a mean length of about 309  $\mu\text{m}$  and a flexed tail that is free of nuclei. They stain well with hematoxylin and Giemsa stains and can be readily identified by a variety of methods. Snips may be taken from any area of the body, but the scapular regions, iliac crests, and outer canthus of the eyes (when nodules are found on the head) are preferred sites. When microfilariae cannot be found in skin snips and onchocerciasis is still suspected, their presence is often revealed as a result of the urticarial reaction that follows a single peroral dose of 50 mg diethylcarbamazine (Mazzotti test).

## **PROGNOSIS**

Onchocerciasis carries considerable associated morbidity, especially chronic and recurrent dermatitis and eye lesions that may affect visual acuity or cause blindness. For example, in the hot, Savannah areas of West Africa, nodules are few in number but the concentrations of microfilariae are high and there is a high rate of visual impairment and blindness. In contrast, in the forest areas of Africa, nodules may be numerous but there is very little blindness. In the endemic areas of Central America, nodules are commonly found on the head; although the skin lesions are not severe, invasion of the eyes by microfilariae and

subsequent loss of visual acuity is an important concern. The patterns of disease in the various parts of northern South America are quite variable.

## **THERAPY**

The surgical removal of nodules (nodulectomy) is widely practiced in Central America but not in Africa, where nodules are scattered over the body surface. Nodulectomy reduces the risk of sight-threatening lesions.

Diethylcarbamazine is widely used for therapy because it is an easily administrable, relatively safe microfilaricidal agent; however, it does not kill adult *O. volvulus*. Diethylcarbamazine should not be used when the microfilarial burden is high or when there are significant numbers of microfilariae in the tissues of the eye because of possible severe side effects, such as severe pruritus, urticaria, and visual problems.

Suramin will kill adult *O. volvulus* but often causes severe adverse reactions, such as renal injury and exfoliative dermatitis. Often, diethylcarbamazine and suramin are used sequentially—first, to reduce the numbers of microfilariae, then to kill the adult worms, leading to resolution of the microfilaremia. Patients should be treated on a case-by-case basis and with direct medical supervision. Mectizan, a new drug derived from ivermectin, a drug used in veterinary medicine, has shown promise in the treatment of onchocerciasis; it is to be distributed in West Africa.

## **PREVENTION**

An insecticide, Abate, is widely used for control of the vector black flies in endemic areas. Alteration of personal behavior and the use of insect repellants to avoid being bitten by *Simulium* species may be preventive.

### **Loiasis (Eyeworm)**

Infection with *Loa loa* is characterized by the presence of the adult filariae in subcutaneous tissues, occasionally in the bulbar conjunctivae, and microfilariae circulating in the peripheral blood during the daytime hours.

## **ETIOLOGY**

Adult female worms reach 7.0 cm in length and have a diameter of about 0.5 mm; male worms are about one-half as large. The adults live and migrate through the subcutaneous tissues of the body, usually without causing symptoms; they may live for as long as 17 years.

## **EPIDEMIOLOGY**

Loiasis is geographically restricted to the rain-forest belt of west and central Africa. Bloodsucking, tabanid flies belonging to the genus *Chrysops* are the vectors. Larvae are transferred to the human host when a vector harboring infective stages of *L. loa*, takes a blood meal. Flies are infected by ingesting microfilariae when they feed on infected humans.

## **MANIFESTATIONS**

Although infection characteristically endures without symptoms, there may be migratory, pruritic swellings on the extremities or in the region of the orbit, the so-called Calabar swellings. These swellings are attributed to the restless, migratory behavior of presumably infertile or unmated female worms and may reflect the host's hypersensitivity to the worms or materials elaborated by them, as evidenced by eosinophilia.

The passage of adult worms through the conjunctivae, though painful and uncomfortable, produces no permanent damage to the tissues.

## **DIAGNOSIS**

Diagnosis is based on the identification of the microfilariae in blood taken during daytime hours. Diagnostic features of the microfilaria include the presence of a sheath, characteristic morphology, and the peculiar distribution of nuclei in the tail.

Adult worms removed from the orbit may be identified on the basis of their morphologic features. A presumptive diagnosis may be made on the basis of Calabar swellings, high eosinophilia, and residence, even for a short period, in an area endemic for loiasis.

## **PROGNOSIS**

Specific treatment or removal of the adult worm(s) from the conjunctivae results in an excellent prognosis.

## **THERAPY**

Diethylcarbamazine kills both microfilariae and adult worms. A peroral dose of 200 mg/day for 20 days constitutes an adequate course of treatment. In patients with high microfilaremia, treatment should begin with low doses. Simultaneous administration of a glucocorticoid during the first 2 to 3 days of treatment is recommended.

## **PREVENTION**

Diethylcarbamazine taken on three days each month in a dose of 200 mg, PO, has been successful in prophylaxis.

## **Mansonella Species**

Two species of the genus *Mansonella*-namely, *ozzardi* and *streptocerca*-may inhabit the subcutaneous tissues of humans and are generally regarded as innocuous parasites-a view not fully documented.

## **MANSONELLA OZZARDI (OZZARDIASIS)**

### **Etiology**

The adult stage of *M. ozzardi* is found in the subcutaneous tissues, and the microfilarial stage circulates in the peripheral blood. The adults are very delicate worms, the females measuring approximately 6 cm in length by 0.16 mm in diameter, while males are much smaller (2.8 x 0.08 mm). Because of its tissue habitat, *M. ozzardi* has been recovered from humans only rarely. Knowledge of its morphologic features is based on experimental infections in primate hosts. Infective larvae develop to the adult stage in about 5 months. The

microfilariae are small (225  $\mu\text{m}$ ) and unsheathed, and circulate in the peripheral blood without any periodicity.

### **Epidemiology**

*Mansonella ozzardi* is found only in tropical America. It is transmitted by blood-sucking gnats (*Culicoides*) in the Caribbean region and by black flies (*Simulium*) and *Culicoides* in the Amazon region of South America.

### **Pathogenesis and Pathology**

Not known.

### **Manifestations**

Infection appears not to cause disease.

### **Diagnosis**

Diagnosis rests on identification of the microfilariae in the peripheral blood.

### **Therapy**

There is as yet no drug that will terminate infection. Diethylcarbamazine does not kill the microfilariae nor does it appear to have any effect on the adult worms.

## ***MANSONELLA STREPTOCERCA* (STREPTOCERCIASIS)**

### **Etiology**

Adult worms are found in the dermal layers of the skin, as are the microfilariae. The former are slender delicate worms; the females measure 25 x 0.07 mm and the males are approximately one-half that size. The microfilariae are small (about 210  $\mu\text{m}$  in length), very slender, lack a sheath, and have a characteristically crooked tail.

### **Epidemiology**

The geographic distribution of *M. streptocerca* is limited to the rain-forests of Africa. *Culicoides* spp have been incriminated as vectors of the parasite.

### **Pathogenesis and Pathology**

Not known,

### **Manifestations**

Because most infected persons lack symptoms, *M. streptocerca* is regarded as innocuous. However, some individuals develop pruritic rashes and papular eruptions in the skin.

### **Diagnosis**

The diagnosis depends on identification of the microfilariae in the dermal layers of the skin. It is important to differentiate *M. streptocerca* from the medically important *Onchocerca volvulus*, which is found in the same regions.

## **Therapy**

Diethylcarbamazine is effective against the microfilariae and adult filariae. Treatment may exacerbate pruritus and skin rashes and is often the cause of papules in the skin from dead and dying adult worms.

## **DRACONTIASIS (GUINEA WORM)**

Infection with the Guinea worm, *Dracunculus medinensis*, results in the development of an ulcerated lesion, usually on the lower extremities, from which the adult female worm protrudes and discharges larvae when it comes in contact with water.

## **Etiology**

The adult worms develop in the subcutaneous tissues and at maturity the female moves to the surface of the skin. Females are long, slender, and fragile, measuring up to 120 cm in length. Males are extremely small, about 40 mm long, and are not usually recovered from the tissues. Larvae produced by the female are discharged in water and are ingested by copepods in which they develop into the infective stage. Humans acquire infection by ingestion of infected copepods. It requires about 1 year for the worms to reach sexual maturity in the human tissues.

## **Epidemiology**

The Guinea worm is present in many parts of Africa and the Middle East and in semi-arid areas of India. The parasite is not endemic in the western hemisphere although related species of *Dracunculus* infect a variety of wild animals. It is unlikely that animals serve as reservoirs of human infection.

## **Manifestations**

As the gravid female worm moves to the surface of the skin, there may be profound systemic symptoms that include pruritus, nausea, vomiting, and giddiness. Lesions usually develop on the feet or ankles but occur elsewhere on the body as well.

## **Diagnosis**

Infection is diagnosed on the basis of the formation of the ulcer, systemic symptoms, and the appearance of the worm in the ulcer.

## **Prognosis**

The prognosis is usually good, although infection may be temporarily disabling. Secondary infections are a common problem.

## **Therapy**

The gradual extraction of the worm from the tissues by winding it on a stick, a few centimeters per day, is still widely practiced. Niridazole, metronidazole, and thiabendazole alleviate symptoms and allow the worm to be removed by traction.

## **Prevention**

Prevention can be accomplished most easily by providing piped water or covered wells, eliminating possible human contamination.

# **LYMPHORETICULAR FILARIASIS**

More than 100 million people are infected with filariae-multicellular roundworms that belong to the phylum Nematelminthes. In contrast with most other nematodes, insects serve as obligatory hosts for some stages of the filariae. Although a diversity of filariae infects mammals, only eight kinds infect humans naturally. Several kinds of filarial infections of humans may be distinguished by distinct predilections of the filariae for particular host organ systems. Both the adult filariae and their larval offspring, the microfilariae, inhabit specific organs depending on the form of filarial infection. For three filariae, the adult forms reside within the lymphatic system, and it is these three-*Wuchereria bancrofti*, *Brugia malayi*, and *Brugia timori*-that are the agents of lymphatic filariasis.

## **ETIOLOGY**

Lymphatic filarial parasites are transmitted to humans by species of mosquitoes that differ with geographic areas and with each of the filariae. Female mosquitoes acquire filariae by ingesting human blood that contains microfilariae. Microfilariae mature over a couple of weeks within the thoracic musculature of the mosquito through successive first, second, and third stage larvae. When the mosquito bites a human, the infectious third stage larvae are released from the mosquito's proboscis and penetrate the puncture site to enter the cutaneous tissues. The larvae mature by undergoing molting to form fourth stage larvae; the adult worms form next, and localize within lymphatic vessels, often proximal to lymph nodes. After fertilization by a male, each female adult releases microfilariae, which enter the bloodstream. Microfilaremia may become detectable 4 months after infection, but usually takes about 8 to 12 months. However, many patients with filariasis will lack detectable microfilaremia. Microfilariae may be sequestered within the vascular beds of the liver, spleen, and lungs, which contributes to periodic fluctuations in the intensity of microfilaremia; greater numbers of microfilariae may be present in the peripheral blood at certain times during a 24-hour period. The mechanism for the periodicity of microfilaremia is poorly understood, but the pattern of circadian periodicity is characteristic of different geographic strains of each of the three filarial species that infect humans.

Adult females of *W. bancrofti* are 80 mm to 100 mm long by about 0.25 mm wide, whereas males are 40 mm long by 0.1 mm wide. Adults of the *Brugia* spp. are smaller. The microfilariae of the three lymphatic spp are sheathed, thereby differing from nonlymphatic spp. Microfilariae are about 250  $\mu\text{m}$  long by about 10  $\mu\text{m}$  wide.

## **EPIDEMIOLOGY**

*Wuchereria bancrofti* is widely prevalent in tropical and subtropical areas of Africa, Asia, the Pacific region, and Central and South America. In the south Pacific, microfilaremia is subperiodic with slightly greater numbers present in the peripheral blood by day than by night; *Aedes* spp. mosquitoes are the principal vectors. In contrast, in most of the rest of the world, *W. bancrofti* microfilariae are nocturnally periodic; almost undetectable in peripheral

blood by day, they gradually increase in numbers in late afternoon, with microfilaremia peaking between midnight and 4:00 A.M.. Night-biting *Culex spp.* mosquitoes are well suited to urban dwelling and are vectors of these strains, as are various species of *Anopheles* mosquitoes. Humans are the only definitive hosts of *W. bancrofti*.

*Brugia malayi* occurs in areas of south and east Asia. The microfilariae are nocturnally subperiodic in the Philippines, Indonesia, and Malaysia, whereas in other areas they are nocturnally periodic. *Mansonia spp.*, *Anopheles spp.*, and other mosquitoes transmit *B. malayi*. *Brugia timori* is the most limited geographically for it is found only on two Indonesian islands.

## MANIFESTATIONS

The manifestations of lymphatic filariasis are variable. Many persons bitten repetitively by mosquitos harboring infective larvae will develop no clinical or parasitologic evidence of active infection. Because it is not possible to detect intralymphatic adult filariae, it is difficult to prove such persons are truly infected.

Among patients with documentable filariasis, the manifestations include asymptomatic microfilaremia, the syndrome of filarial fevers, lymphoobstructive lesions, and tropical pulmonary eosinophilia.

### Asymptomatic Microfilaremia

Infected persons have no clinical evidence of filariasis but have microfilaremia with levels ranging from less than 1 microfilaria/ml to more than 10,000 microfilariae/ml of blood.

### Filarial Fevers

The commonest symptomatic manifestation of lymphatic filariasis is the occurrence of repeated inflammatory paroxysms that are referred to as “filarial fevers.” Typically, these episodes consist of fever, lymphadenitis, and lymphangitis. An attack usually begins with the onset of pain referred to lymph nodes or lymphatic vessels, often in the upper or lower extremities. Chills and fever develop within hours. The fever may be pronounced and may be accompanied by rigors early in the episode. Regional lymph nodes may become enlarged and inflamed. Lymphadenitis may be very apparent in or femoral areas and may also occur in retroperitoneal and intraabdominal nodes. Involved nodes may suppurate and, more commonly with brugian than bancroftian filariasis, may extend through the skin to produce lesions that heal slowly with scarring. If lymphangitis develops, it characteristically evolves in a retrograde fashion progressing distally along the course of the lymphatic. Lymphangitis may be accompanied by thrombophlebitis and may be manifest as a tender palpable cord, as a linear erythematous streak along the course of the vessel, or as blotchy erythematous areas over the lymphatic channel. In bancroftian filariasis, lymphangitis in males may cause episodes of funiculitis, epididymitis, and testicular pain. Constitutional symptoms, including nausea, vomiting, and abdominal pain, may accompany episodes of filarial fevers. The paroxysms of filarial fevers are self-limited, often lasting for 2 to 3 days, but ranging from 1 to 10 days. Recurrences of attacks of filarial fevers are typical, occurring several times a year for many years in some patients.

### Tropical Pulmonary Eosinophilia

The pulmonary eosinophilic form of lymphatic filariasis has been recognized most commonly in the Indian subcontinent and in Southeast Asia where it afflicts males more often than females. The usual manifestations are dyspnea and asthmatiform episodes with wheezing

or cough that may be more pronounced at night. Fever, weight loss, and lymphadenopathy may accompany the respiratory manifestations or may be present at the outset.

## DIAGNOSIS

The definitive diagnosis of filariasis is made by identifying microfilariae in the blood. Except for patients from Pacific areas with subperiodic filaremia, nocturnally periodic microfilariae are best detected either in blood specimens obtained at night or in daytime blood specimens obtained about an hour after the administration of a provocative dose of 100 mg diethylcarbamazine (which elicits a transient release of microfilariae into the blood). Although microfilariae may be detected in the small volumes of blood used to prepare smears, sensitivity is increased by examining milliliter volumes of blood using filtration (Nuclepore membrane filters with 3  $\mu$ m pores). Microfilariae retained on the filter may be stained and quantitated; however, morphology is more easily assessed in blood smears. The pattern of staining of nuclei aids in speciation of the sheathed microfilariae: *Brugia* spp. have nuclei that extend into the tail and end with two distinct caudal nuclei, whereas *W. bancrofti* lack caudal nuclei.

The absence of detectable microfilariaemia does not exclude a diagnosis of filariasis, especially in patients with lymphoobstructive disease, who typically have little or no microfilariaemia. Serologic tests for antifilarial antibodies are available, but must be interpreted with caution because most long-term residents of regions endemic for filariasis will be seropositive. In patients with filarial fevers, the diagnosis may have to be based on the clinical features of the episodes, the history of multiple recurrences, and the exclusion of other etiologies for self-limited febrile episodes.

In tropical pulmonary eosinophilia, eosinophilia in the peripheral blood will often be higher than in the other clinical forms of filariasis. The total serum IgE will be markedly elevated, usually > 5000 ng/ml, and antifilarial antibodies often attain high titers. Roentgenograms of the chest may reveal increased bronchovesicular markings, the presence of multiple small (several mm in diameter) miliary lesions, or mottled opacities. These radiographic findings may be subtle or absent. Pulmonary function tests may initially show obstructive changes, but most patients have restrictive defects that become more prominent with chronicity. Although microfilariae are usually not detectable in the blood, the clinical and radiographic features in a patient from an endemic area, together with the results of blood and serologic tests, help distinguish this syndrome from asthma and from other eosinophilic syndromes with pulmonary involvement.

## PROGNOSIS

In patients with filarial fevers, recurrent episodes contribute to lymphatic damage. Removal of patients from tropical to temperate areas is often associated with a cessation of episodes of fever. The progressive evolution of elephantiasis causes major deformities of involved regions. Pulmonary fibrosis develops if tropical pulmonary eosinophilia goes untreated.

## THERAPY

Lymphatic filarial infections are treated with diethylcarbamazine citrate (DEC). The mechanism of action of diethylcarbamazine remains uncertain. Through an opsonin-like effect, diethylcarbamazine facilitates the killing of microfilariae in vivo but is not toxic to them in vitro; moreover, whether it is lethal to adult filariae in patients is uncertain. Diethylcarbamazine is usually given for 2 weeks (5-6 mg/kg body wt/day, PO, either as a

single dose, or in three equal portions, 8-hourly). Although microfilaremia clears rapidly after the first dose, microfilariae may again become detectable in the weeks following a course of therapy. Treatment may need to be repeated and given for several weeks. Adverse reactions are more likely to occur early in treatment and in patients with high numbers of microfilariae; hence, it is suggested that treatment begin with dosage of 2 mg/kg body wt/day. The adverse effects include fever, chills, headache, and nausea and vomiting.

### **PREVENTION**

The prevention of filariasis requires limiting exposure to mosquito-borne infective larvae. In endemic regions, area control of mosquitoes should be undertaken. Personal measures, such as repellents and mosquito netting, may have some utility in limiting mosquito bites. It is not known if taking diethylcarbamazine is prophylactic against lymphatic filariasis. Mass treatment of populations with the drug has been used to diminish microfilaremia, and consequently, the likelihood of mosquito-borne transmission of infection.

### **REMAINING PROBLEMS**

The immunopathogenesis of the various manifestations of filariasis is poorly understood. Therapy with diethylcarbamazine remains imperfect. Agents are needed that will kill adult worms and eradicate microfilariae without eliciting adverse effects. A major goal is the development of medically and economically feasible immunotherapeutic or chemotherapeutic measures for application in humans, along with vector control approaches, to interrupt the transmission of filariae in endemic areas.

### **ZOONOTIC FILARIAE**

Humans are exposed to arthropods bearing infective larvae of filarial species that are naturally parasitic for nonhuman mammalians. If the zoonotic filariae develop in the unnatural human host, the adult filariae manifest the same organ tropism and localize in the same organs as they do in their natural hosts. Thus, the adult form of *Dirofilaria immitis* (dog heartworm) localizes in the right ventricle and pulmonary arteries of the natural canine host; in the human, adult *D. immitis* also localize in pulmonary arteries and elicit focal pulmonary arteritis with the formation of granulomas. While a minority of patients may have low-grade eosinophilia or hemoptysis, most patients with zoonotic dirofilariasis are asymptomatic and are detected when a coin lesion is found on roentgenographic examination of the chest. Excisional biopsy, often done to exclude a neoplasm, is diagnostic and curative.

Adult forms of zoonotic *Brugia* spp. inhabit lymphatic vessels in animals: in humans, the adult *Brugia* spp. have been found in excised lymph nodes of patients with focal lymphadenopathy.

Because microfilariae are not produced in humans parasitized by zoonotic filariae, treatment with diethylcarbamazine is not necessary.

## **SNAKE BITES**

Snakes are to be found in most parts of the world, but only around 15 per cent of the 3000 or so different types of poisonous snakes that exist are regarded as posing a potential risk to humans. Most of these are to be found in

- tropical and subtropical region
- across most of the United States (except Alaska, Maine and Hawaii)
- Australia.

Despite the many stories about constrictors, particularly anacondas in the Amazon and pythons in the East, which are said to have strangled adult humans, these need to be treated with a great deal of scepticism. In practice it is only the poisonous snakes that are of interest.

### **Epidemiology: Incidence (US)**

- A. Total: 45,000 snake bites in U.S. per year
- B. Venomous bites: 8000 in U.S. per year
- C. Deaths from snake bite in U.S.: 12 or less per year
- D. Envenomation occurs in 75% of U.S. poisonous snakebites

### **Etiology: U.S. Poisonous snakes**

- A. Coral Snakes (Family Elapidae)
  - 1. Nonaggressive snakes of the southern U.S.
  - 2. Transfer venom via chewing instead of injection
- B. Pit Vipers or Crotalidae (99% U.S. venomous bites)
  - 3. Rattlesnake (Crotalus or Sistrurus genera)
    - a. Most common poisonous snake in U.S.
    - b. Potent venom
    - c. Responsible for 95% of deaths (esp. Diamondback)
  - 4. Cottonmouth, water moccasin (Agkistrodon piscivorous)
    - a. Aggressive water snakes in Southeastern U.S.
    - b. Moderately potent venom
  - 5. Copperhead (Agkistrodon contortrix)
    - a. Least potent venom

### **How to avoid snake bites?**

- Wear long boots and trousers (which in rainforests also provide some protection against leeches).

- Make a noise (or to be more correct vibrations in the surroundings - snakes are deaf, but react to 'shaking'). Beat and bash with a long branch or twig in the area three to five paces ahead, and stand still for a short time before taking the next step. By far the majority of snakes prefer to flee if given the chance. An exception is the uncontrollably aggressive Australian Taipan, which also strikes out unpredictably. Puff adders are very quiet but dangerous snakes, if you see one sneak way with as little noise as possible.
- Avoid going out in a snake area in darkness. If it is necessary to do so, then take a strong torch with you. Snakes prefer to evade bright light and vibrations.
- If you see a snake, you should stand completely still. It will instinctively prefer to go away and most snakes predominantly attack moving targets.
- Do not put your hands down into holes, dark cavities or cracks in rock, even if something has fallen down it. To reclaim anything, you can attempt to fish it out with a stick, standing well away from the hole. Creepy-crawlies other than snakes (for example scorpions) may also be poisonous, and they are all lightning fast.
- The best possible advice is not to touch a snake in the wild. The worse thing you can do is try to pick one up so that the doctor can identify it! If you see a 'dead' snake, you should keep well clear. Many people have been bitten two or three times by 'dead' snakes. Only if someone has been bitten should you make sure that the snake is killed and take it along for identification, but hold it by its tail and continue to watch out for its head, or preferably put it in a sack that can be held away from the body.
- All sea snakes (Hydrophiidae) are potentially extremely poisonous and snorkellers and scuba divers should not attempt to inspect them more closely. Sea snakes typically occur on the coasts of south-east Asia and Australia.

### **Symptoms and danger signals**

The risk of snake bites depends on many factors, such as:

- the species and size of the snake.
- the amount of venom injected.
- the number of bites.
- the localisation of the bites (bites in the head or on the body are most dangerous, but the bites will typically be on arms or legs).
- the weight of the victim (most dangerous for children).
- the general state of health of the victim.
- individual sensitivity to the venom.

Symptoms with rapid onset:

- local pain, swelling and discolouration at the site of the bite are to be expected, but may not arise immediately after the bite (for example the bite of the coral snake will rarely cause immediate local reactions), and the general reactions often do not appear until 8 to 24 hours have elapsed).
- within the first 10 to 15 minutes to a few hours after the bite has occurred, general symptoms may appear such as a sense of anxiety, malaise, vomiting, headache, dizziness, bouts of sweating, respiratory distress, bleeding, heart failure and shock, muscle contractions, confusion, convulsions, paralysis, unconsciousness and death.

Symptoms with later onset (often 6 to 24 hours after a bite):

- local (around the site of the bite): increasing and massive swelling of the whole arm, even if the bite wound is located right out on the hand. Blistering and bleeding often occur in the skin and tissues just below it, and muscles. Blood clots may occur in the surrounding blood vessels. Necrosis (tissue death) of skin, connective tissue and muscles is an evident risk.
- general symptoms: increasing grogginess, vomiting, respiratory difficulties, fever, falling blood pressure and shock. Bleeding from the mucous membranes (eg the gums), bloody vomit and stool and blood in the urine may also occur. Disturbances of sensation or paralysis may occur, often first in the face and later in the muscles involved in swallowing and breathing.

In principle, snake venoms act in three 'different' ways:

- haemotoxins, ie venoms that split (haemolyse) the red blood cells, or affect the ability of the blood to clot (coagulate).
- neurotoxins, ie venoms that in particular paralyse nerve transmission to the muscles and in the worst case paralyse the muscles involved in swallowing and breathing.
- cardiotoxins, ie venoms that have a direct harmful action on the heart and lead to circulatory failure and shock.

But as a number of other factors, including possible allergic reactions, are also involved in poisoning, the situation is often far more complex and unclear, and there are often typically 'mixed' reactions and symptoms.

**IMMEDIATELY FOLLOWING A SNAKE BITE:**

1. Try to safely and quickly identify the species of snake if practical. Move victim to safety. Have one person take firm command of the situation very early to improve the coordination and decision making processes. The victim's condition is assisted with an observation that calm and competent assistance is being firmly applied. There will be no time for shy or timid behavior! Action will be crucial! Proceed with no delay to use judgment calls on all of the below suggested techniques.

2. Remove any jewelry or tight fitting clothing. Quickly tie a light restricting band both above and below the bite area a few inches away from the puncture/bite marks.
3. Without cutting, apply strong suction, preferably within seconds of the bite directly on the main or deepest puncture/bite marks. This can be accomplished with the mouth or a commercial bite kit suction device. Time is critical here as any venom present will become destructive very quickly!
4. Rapidly apply antiseptic cleanser to the entire area and place cold compress as closely as possible without interfering with suction process.
5. Continue strong suction and alternate the location of compress to avoid injury from severe cold.
6. Check constriction bands periodically as swelling may occur and loosen as appropriate.
7. Monitor for symptoms of shock and be prepared to administer appropriate treatment. At any signs of major stress or unusual/unexplained discomfort, check for need to apply other first aid techniques - elevate bitten extremity, elevate legs from lying down position, keep warm, immobilize, etc. Do not administer alcohol or cause additional stress to victim. Avoid food or liquid intake.
8. Keep victim warm and immobilize as practical. Movement to proper treatment facility is more crucial than maintaining immobile status. Maintain above treatment functions throughout.
9. Transport safely at the earliest possible time to competent medical service. Ideally, all of the above steps can be administered concurrently with transport phase. Keep victim as comfortable as possible and reassure that survival is not in question. Rapid response reduces damage levels.
10. If possible and *voluntarily chosen*, administer electroshock to bite area in several one second bursts in a small circle around bite. Repeat this at 10-15 minute intervals getting slightly farther from bite area seeking to follow course of venom flow. Take care to utilize DC current at proper levels and prepare in advance to administer this technique.
11. If practical, dispatch snake and take along for any identification or testing needs. The primary purpose of this first aid is to slow down or reduce the invasion of the venom, to protect the victim from further side effect trauma, to prepare the victim for later medical procedures such that complications may be minimized, and generally to get the victim to such treatment as quickly and safely as practical.
12. Stand by for back up assistance or side task assignments like contacting relatives, protecting scene materials, providing useful information of incident facts, describe first aid administered, etc.
13. Be confident that all which could have been done was applied to assure as successful an outcome as possible given that a venomous bite is difficult to control or establish a completely accurate prognosis. Remember, early treatment is better treatment when such a bite occurs!

### **What NOT To Do if You or Someone Else is Bitten by a Snake**

- Do not pick up the snake or try to trap it (this may put you or someone else at risk for a bite).
- Do not apply a tourniquet.
- Do not slash the wound with a knife.
- Do not suck out the venom.
- Do not apply ice or immerse the wound in water.
- Do not drink alcohol as a pain killer.
- Do not drink caffeinated beverages.

#### **Vaccinations**

Snake venoms cannot be vaccinated against, but everyone, particularly those who travel, should be sufficiently vaccinated against tetanus and diphtheria within the last 10 years. Although constrictors are not poisonous, both their bites and the bites of poisonous and non-poisonous snakes can cause infections, including tetanus.