

African Trypanosomiasis

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Introduction

Definition

African trypanosomiasis is infection by protozoan hemoflagellates of the *Trypanosoma brucei* complex, 2 subspecies of which cause disease in humans: *Trypanosoma brucei gambiense* causes Gambian (chronic) trypanosomiasis and *Trypanosoma brucei rhodesiense* causes Rhodesian (acute) trypanosomiasis. A third economically important subspecies, *Trypanosoma brucei brucei*, causes nagana, a fatal disease of animals, but does not infect humans.

Synonyms

Synonyms include African sleeping sickness, human trypanosomiasis, Gambian sleeping sickness/West African trypanosomiasis (*T. b. gambiense*), Rhodesian sleeping sickness/East African trypanosomiasis (*T. b. rhodesiense*), *maladie du sommeil*, and *sonolencia*.

General Considerations

The first trypanosomes to be described were nonpathogenic species in the frog (Gruby 1843) and the rat (Lewis 1878). In India in 1880, Evans first attributed a disease to trypanosomes—surra, a disease of horses, mules, camels, and cattle.

African trypanosomiasis has probably played an impor-

tant role in recorded history from antiquity dating to the 2nd millennium BC.¹

African sleeping sickness was clearly recognized as early as the 14th century in a Sudanese king.² Winterbottom, in his “Account of the Native Africans in the Neighborhood of Sierra Leone” (1803), described the disease incidentally.³ During his travels in southern Africa (1840-1856), David Livingstone gave a detailed account of a disease afflicting animals bitten by the tsetse fly, noting on one occasion that “we lost forty-three fine oxen by its bite.”⁴ In 1894 Bruce observed *T. brucei* in the blood of a cow with nagana in Zululand (South Africa), and demonstrated that the disease was transmitted to cattle from big game animals by *Glossina morsitans*, a biting fly. In 1901, Dutton found trypanosomes in the blood of a patient with Gambia fever and named the organisms *T. gambiense*. Two years later, Castellani found identical organisms in the spinal fluid of 5 patients with African sleeping sickness. Bruce and Naborro demonstrated that the tsetse fly was the vector of the trypanosomes, and that Gambia fever and sleeping sickness were 2 stages of the same disease.⁵ In 1910, Stephens and Fantham identified trypanosomes in the blood of a patient in Rhodesia (now Zambia and Zimbabwe). *Trypanosoma rhodesiense* was later determined to be indistinguishable from *T. brucei*.⁶

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Three severe epidemics of African trypanosomiasis have been recorded since the late 19th century, the first in Uganda and the Congo Basin between 1896 and 1906. A second epidemic in the 1920s swept through several African countries and was arrested by systematically screening millions of people. African trypanosomiasis practically disappeared between 1960 and 1965, but has reappeared in endemic form in several foci since 1970 as a result of political and socioeconomic instability, diminishing measures for vector control and surveillance for the disease.^{7,8} In the Democratic Republic of the Congo (DRC), this lack of active control measures has resulted in a resurgence of sleeping sickness, with rates of infection similar to those of the late 1920s.⁹ The importance and impact of sociopolitical factors on the incidence of African trypanosomiasis was investigated quantitatively and qualitatively using data from 35 affected countries in Sub-Saharan Africa.¹⁰ Statistical analytical methods showed an association between civic/political conflicts and changes in the geographical incidence of human African trypanosomiasis.

Epidemiology

Trypanosoma brucei is limited to tropical Africa, where it is widely distributed throughout the tsetse-fly belt, a 10-million-square-mile area stretching from 15° N to 20° S of the equator (Fig 3.1) (Table 3.1). *Trypanosoma brucei gambiense* infects humans in foci within a wide range in western and central Africa and Angola. Endemic foci of *T. b. rhodesiense* infections are found in limited areas of eastern and southern Africa. Within this range, the disease is distributed unevenly because the vector is usually confined to rural areas, in dense vegetation along streams and lakes (*T. b. gambiense*) (Fig 3.2), or wooded areas of the savanna (*T. b. rhodesiense*). Moreover, within endemic countries there are many regions where parasite-free tsetse flies are found. A focus of disease can be a single village or an entire region, and the intensity of disease can vary considerably from village to village. Epidemics are typically followed by long periods of endemicity.¹¹ Occasionally, imported sleeping sickness is reported in a nonendemic country.¹²

At least 60 million Africans are at risk of infection, but only 4 million are under surveillance.⁷ Approximately 45 000 cases were reported in 1999, but the World Health Organization estimates that the number of patients was between 300 000 and 500 000. Due to inadequate health care, only 10% of new sleeping sickness patients are diagnosed and treated.⁷ Many die before they are diagnosed. African trypanosomiasis is the leading cause of death in some endemic areas, ahead of HIV/AIDS.

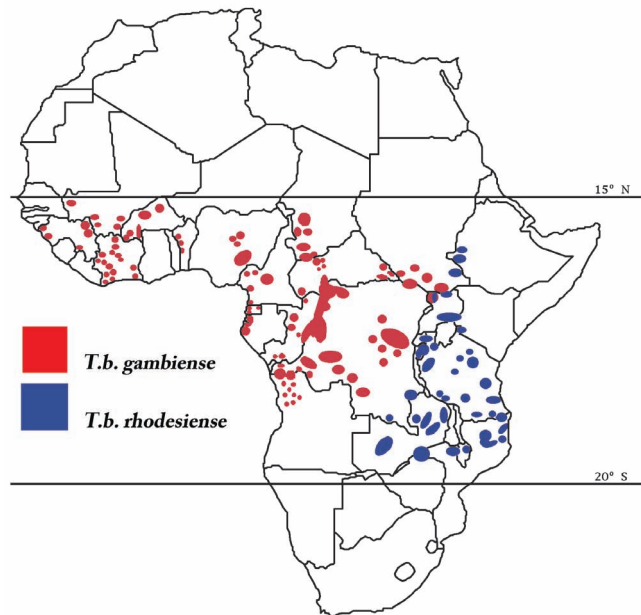


Figure 3.1
Focal distribution of African trypanosomiasis in humans.
(Modified from WHO Technical Report Series 739, 1986.)



Figure 3.2
Tributary of Lopori River (1° N lat.) near Bongandanga in Gambian trypanosomiasis-endemic area of northwestern Democratic Republic of the Congo. Note forested terrain with underbrush and grass overhanging riverbank. Tsetse flies bit the photographer many times during the brief ferry crossing.

Nation	Level of endemicity	Subspecies
WESTERN AFRICA		
Benin.....	Low.....	<i>gambiense</i>
Burkina Faso.....	Low.....	<i>gambiense</i>
Côte d'Ivoire.....	High.....	<i>gambiense</i>
Ghana.....	Low.....	<i>gambiense</i>
Guinea.....	High.....	<i>gambiense</i>
Guinea Bissau.....	Low.....	<i>gambiense</i>
Liberia.....	Unknown.....	<i>gambiense</i>
Mali.....	Low.....	<i>gambiense</i>
Senegal.....	Unknown.....	<i>gambiense</i>
Sierra Leone.....	Unknown.....	<i>gambiense</i>
Togo.....	Low.....	<i>gambiense</i>
NORTHEASTERN AFRICA		
Chad.....	High.....	<i>gambiense</i>
Ethiopia.....	Unknown.....	<i>rhodesiense</i>
Sudan.....	Epidemics.....	<i>gambiense</i>
CENTRAL AFRICA		
Burundi.....	Unknown.....	<i>rhodesiense</i>
Cameroon.....	High.....	<i>gambiense</i>
Central African Republic.....	High.....	<i>gambiense</i>
Congo.....	High.....	<i>gambiense</i>
Democratic Republic of the Congo.....	Epidemics.....	Both
Equatorial Guinea.....	Low.....	<i>gambiense</i>
Gabon.....	Low.....	<i>gambiense</i>
Kenya.....	Low.....	Both
Nigeria.....	Unknown.....	<i>gambiense</i>
Rwanda.....	Unknown.....	<i>rhodesiense</i>
United Republic of Tanzania.....	High.....	Both
Uganda.....	High.....	<i>rhodesiense</i>
SOUTHERN AFRICA		
Angola.....	Epidemics.....	Both
Botswana.....	Unknown.....	<i>rhodesiense</i>
Malawi.....	Low.....	<i>rhodesiense</i>
Mozambique.....	High.....	<i>rhodesiense</i>
Namibia.....	Unknown.....	Both
Zambia.....	Low.....	<i>rhodesiense</i>
Zimbabwe.....	Low.....	<i>rhodesiense</i>

Table 3.1

African nations within geographic range of trypanosomiasis. Note: Different periods covered account for slight differences in data presented in this table and the map in Figure 3.1.

Infectious Agent

Morphologic Description

Trypanosoma brucei gambiense and *T. b. rhodesiense* are morphologically indistinguishable. In fresh blood or cerebrospinal fluid (CSF), the parasites appear as colorless flagellates. Trypomastigotes, the only stage found in human hosts, are polymorphic and circulate in 3 distinct forms: 1) a long slender form, usually with a blunt posterior end, a subterminal kinetoplast, and a long free anterior flagellum (Fig 3.3); 2) a short stumpy form, usually with a round or pointed posterior end, a terminal kinetoplast, and a short or absent free flagellum (Fig 3.4); and 3) a spectrum of intermediate forms whose morphologic features vary considerably. Stained flagellates are 14 to 33 μm by 1.5 to 3.5 μm . They have a large, oval, centrally placed red or violet nucleus that occupies as much as one quarter of the organism (Fig 3.5). A tiny spherical kinetoplast near the posterior end is composed of a parabasal body and a blepharoplast,



Figure 3.3
Trypomastigote of *Trypanosoma brucei rhodesiense* in blood film from American traveler who visited East Africa 10 days previously. Long slender form is characterized by blunt posterior end, tiny spherical subterminal kinetoplast, large centrally placed nucleus, and long free flagellum. Flagellum extends posteriorly along outer border of undulating membrane. Giemsa x1300

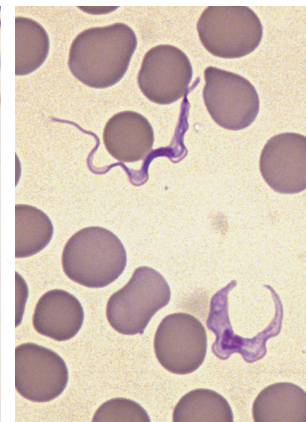


Figure 3.4
Long slender form and short stumpy form of *Trypanosoma brucei rhodesiense* in blood film from patient described in Figure 3.3. Note absence of kinetoplast and free flagellum in stumpy form. Giemsa x1240

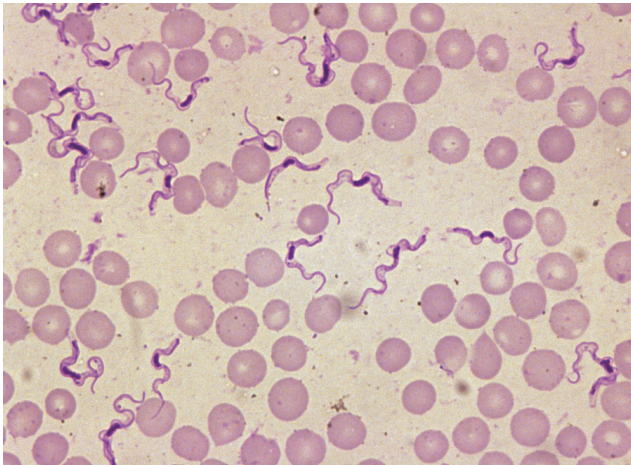


Figure 3.5
Trypomastigotes of *Trypanosoma brucei gambiense*, morphologically indistinguishable from *Trypanosoma brucei rhodesiense*, in blood film from experimental infection. Giemsa x725

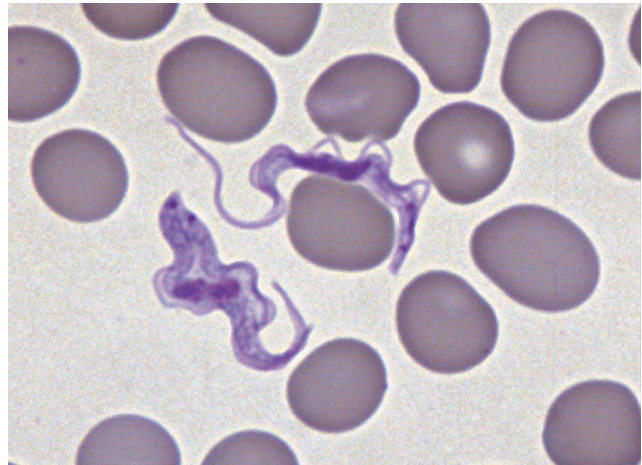


Figure 3.6
Two trypomastigotes of *Trypanosoma brucei rhodesiense* dividing by binary longitudinal fission in blood film of patient described in Figure 3.3. Division is more advanced in parasite at bottom. Giemsa s1800

structures rarely identified by light microscopy. Ultrastructural studies show that the kinetoplast is continuous with a single long mitochondrion that occupies much of the core of the parasite, and that it is intimately associated with the blepharoplast. The nucleus and kinetoplast are dark with Giemsa, Romanovsky's, and Wright's stains. Numerous blue or grayish violet granules are usually scattered throughout the pale blue cytoplasm. A rather broad undulating membrane originates on the posterior end of the body and makes several undulations. The axoneme arises from the blepharoplast, continues anteriorly along the outer border of the undulating membrane, and becomes a free flagellum at the anterior end. African trypanosomes divide by binary longitudinal fission (Fig 3.6).

Life Cycle and Transmission

The life cycle of African trypanosomes is depicted in Figure 3.7. African trypanosomiasis is transmitted by males and females of several species of *Glossina*, the tsetse fly (Figs 3.8 and 3.9). A single fly can be infected with more than one species of trypanosome, and an infected fly remains infected for life.¹³ The fly ingests trypomastigotes in a blood meal from an infected mammal. Once inside the fly, parasites have a life cycle of 3 to 5 weeks. Organisms multiply within the insect gut. They penetrate the epiperitropic space where they undergo binary fission, then migrate to the salivary glands where they first become epimastigotes that attach to microvilli of salivary epithelial cells by flagellipodia. While thus attached, epimastigotes develop successively into

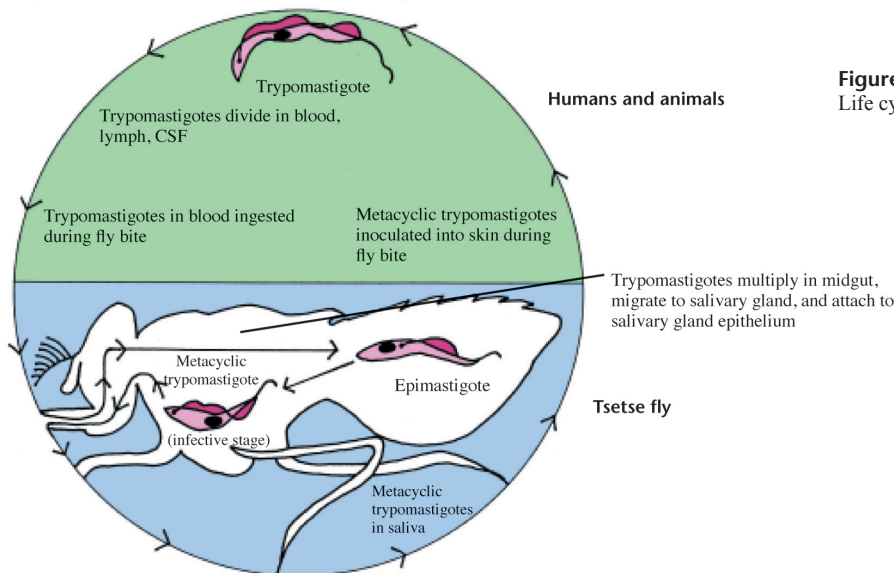


Figure 3.7
Life cycle of African trypanosomes.



Figure 3.8
Insectary-reared tsetse fly (*Glossina morsitans*) biting skin of rodent. At rest, wings are folded scissor-like over dorsum.

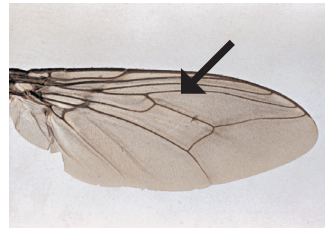


Figure 3.9
Tsetse-fly wing showing unique "hatchet" or "cleaver" cell venation (arrow).

premetacyclic, then nascent metacyclic trypomastigotes. In the final stage, mature metacyclic trypomastigotes detach from salivary epithelial cells and are free in the saliva.¹⁴ When the fly takes another blood meal (Fig. 3.8) mature metacyclic trypomastigotes (the infective stage) in the fly's saliva are inoculated into a new host. Infection can be established by as few as 10 trypanosomes. The parasites remain at the bite site for 1 or 2 days, during which time they multiply and begin to spread to the host's blood and extracellular fluids. Some enter interstitial elements of tissues, especially in the lymph nodes and brain, where they multiply rapidly by binary fission. Intracellular forms (amastigotes) similar to those of *Trypanosoma cruzi* have been reported in the choroid plexus of experimentally infected rodents,^{15,16} but have never been demonstrated in human tissue.

Trypanosoma brucei gambiense can infect domestic animals such as pigs, goats, and sheep, but humans are the most significant host.¹⁷ In humans, *T. b. gambiense* causes a chronic infection that can last for years, allowing infected travelers to introduce sleeping sickness into areas previously free of the disease. Infection with *T. b. rhodesiense* is more rapidly fatal and therefore less likely to spread to nonendemic areas. Wild game animals such as bushbucks and hartebeests are the natural hosts of *T. b. rhodesiense*, although carnivores, cattle, and some other ungulates also serve as hosts.

Trypanosomes can cross the placenta and infect the fetus, causing abortion, stillbirth, or neonatal death.¹⁸ They are rarely transmitted by laboratory accident, blood transfusion, or organ transplantation.

Clinical Features and Pathogenesis

African trypanosomiasis has been described as a disease of exceptions because its clinical picture is protean. Asymptomatic carriers of both *T. b. gambiense* and *T. b. rhodesiense* have been recorded,¹⁹ but without treatment, virtually all patients with African trypanosomiasis die. Gambian and Rhodesian trypanosomiasis have similar clinical features, but differ significantly in the course of disease. Rhodesian

trypanosomiasis becomes symptomatic 1 to 3 weeks after infection, develops rapidly, is more disabling, and often causes death within 3 to 6 months in an untreated patient. Gambian trypanosomiasis causes chronic infection with a more prolonged course (Fig 3.10). Classically, both forms of the disease develop in 3 clinical stages: chancre (Fig 3.11), hemolymphatic invasion, and meningoencephalitis.²⁰ Chancres are more common in Rhodesian than in Gambian trypanosomiasis, but this stage is often bypassed.

A tsetse-fly bite can be painful and may incite almost immediate inflammation. Between 20% and 50% of patients develop a chancre at the site of inoculation 1 to 2 weeks



Figure 3.10
Moribund, emaciated Congolese in terminal stage of Gambian trypanosomiasis.



Figure 3.11
Trypanosomal chancre in American who traveled to East Africa. Patient developed severe Rhodesian trypanosomiasis.

after being bitten (Fig 3.11).²¹ Initially, the chancre is a cutaneous nodule up to 4 cm in diameter, which may ulcerate and persist for 2 to 3 weeks, then resolve spontaneously. At this stage, differential diagnosis includes various cutaneous nodular lesions, including anthrax or tick bite associated with *Rickettsia conorii* infection.

The chancre is followed by a hemolymphatic stage, during which parasites disseminate through the lymph nodes, lymphatic system, and bloodstream. Symptoms include fever, malaise, generalized rash, headache, myalgia, arthralgia, pruritus, transient (mostly facial) edema, lymphadenopathy (Fig 3.12) splenomegaly, and hepatomegaly. In patients with Rhodesian trypanosomiasis, this stage may be fulminant, following development of the chancre by only a few days. Lymphadenopathy is common in both Rhodesian and Gambian trypanosomiasis, but enlargement of the posterior cervical lymph nodes (Winterbottom's sign) is typical of the Gambian form (Fig 3.12). It is considered a sign of peripheral trypanosomiasis without cerebral involvement; however, there is evidence of a connection between these lymph nodes and the ventricles of the brain.²² Lymphadenopathy associated with the Rhodesian form is often more generalized and more frequently accompanied by hepatosplenomegaly. Some patients with Rhodesian trypanosomiasis die at this stage, before the central nervous system (CNS) becomes involved; in other patients the hemolymphatic and meningoencephalitic stages overlap.

The meningoencephalitic, or neurologic, stage begins when the parasite crosses the blood-brain barrier into the CNS. Rhodesian trypanosomiasis progresses to this phase 3 weeks to 2 months after infection.²³ Sleep cycle disturbances are a hallmark of the disease and the source of the term sleeping sickness. Other symptoms include headache, sensory disturbances, poor coordination, and mental and physical lethargy. Psychological and behavioral changes may precede clinical neurologic signs such as tremor, fasciculation, athetosis, cerebellar ataxia, and signs of meningitis or encephalitis. There are few focal neurologic signs, such as cranial nerve palsies, and seizures are rare. Patients who do not receive treatment before the onset of the terminal phase of disease experience irreversible neurological damage. Mask-like facies develop and patients become increasingly obtunded. Loss of consciousness, coma, and death follow, often as a result of pneumonia or other complications of coma (Fig 3.10). The fatality rate for patients who receive optimal treatment is approximately 6%.²³

Adult female patients may experience menstrual disturbances, infertility, and spontaneous abortions; adult male patients may become impotent.¹⁸ Specific trypanosomal myocarditis is more common and more severe in the Rhodesian form, but the diagnosis is usually not established until the patient's tachycardia, hypotension, and congestive heart failure are reversed by specific antitrypanosomal therapy. Some patients have electrocardiographic abnormalities.²⁴

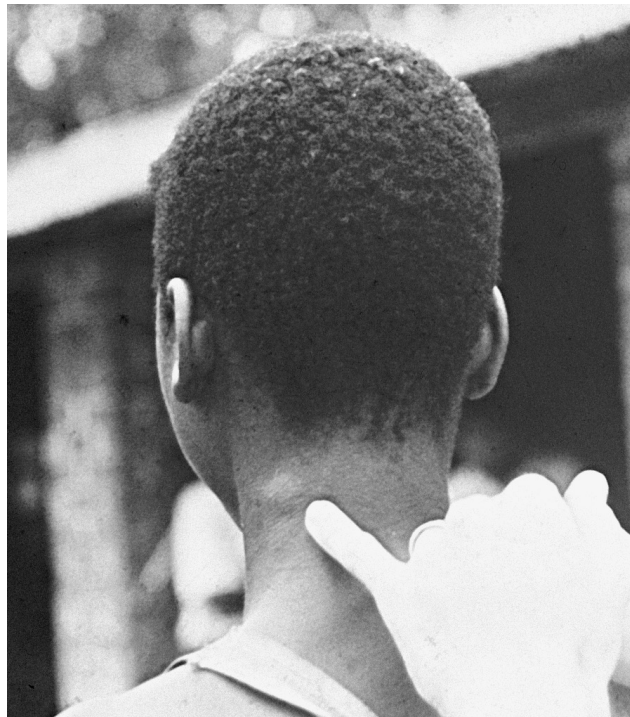


Figure 3.12

Cervical lymphadenopathy in Gambian trypanosomiasis (Winterbottom's sign).

Clinical laboratory findings include normochromic normocytic anemia,²⁵ thrombocytopenia,²⁶ granulocytopenia, and elevated sedimentation rate and immunoglobulins, especially IgM. The CSF contains increased protein and mononuclear cells (about 5% of which are plasma cells), and often trypanosomes. The majority of lymphocytes in the CSF are B-cells.²⁷

Most animal trypanosomes are lysed effectively in the human bloodstream and do not cause disease.²⁸ A high percentage of trypanosomes that are pathogenic for humans are removed from the bloodstream by macrophages in the liver.

Trypanosomes escape the host immune response by a variety of mechanisms.²⁹ *Trypanosoma brucei gambiense* and *T. b. rhodesiense* evade the human immune system by periodically changing their variable surface glycoprotein (VSG) through a complex and poorly understood genetically controlled mechanism.³⁰⁻³² VSG stimulates a pronounced proliferation of B-lymphocytes, first within lymph nodes and then within the brain and meninges, resulting in marked hypergammaglobulinemia dominated by IgM and antibodies that lyse trypomastigotes. Antigen-antibody complexes circulate and may be deposited in tissues.²⁰ New insights gained into the role lipids play in various biological processes have shown apolipoprotein L-1 (ApoL-1) as an intracellular trigger of trypanolysis through the formation of anionic pores on lysosomal membranes that allow the massive influx of chloride ions from the blood stream

into the lysosome causing uncontrolled swelling and the ultimate death of the parasite, thus providing an alternative mechanism for the host to reduce the circulating trypanosome burden.³³ Neutralization of the ApoL-1 effect has been shown to be the dominant factor by which *T. b. rhodesiense* resists trypanolysis. In addition the number of organisms in the bloodstream varies in cycles lasting several days, corresponding to changes in the antigenicity of the VSG, which allows trypanosomes to evade the thymus-dependent humoral response. Transfer of VSG from trypanosomes to host cells, such as erythrocytes, may contribute to pathogenic effects such as anemia.²⁵ The parasite causes generalized host immunosuppression. Thrombocytopenia may be a result of splenomegaly or, in some patients, disseminated intravascular coagulopathy.²⁶ HIV infection does not appear to have a significant impact on the risk of infection with *T. b. gambiense*.³⁴

The immune response produces cytokines and nitric oxide that damage pericytes and break down the blood-brain barrier, allowing inflammatory cells and trypomastigotes to invade perivascular spaces.³⁵⁻³⁸ Encephalitis causes demyelination which, in certain areas of the brain, results in derangement of the internal “clock” that regulates sleeping and waking. The term sleeping sickness refers to this disruption of normal circadian rhythms.³⁹

Pathologic Features

Histologic examination of the chancre shows lymphocytic vasculitis involving the dermal blood vessels, plump proliferating endothelial cells, and an intense perivascular mononuclear cell infiltrate with occasional eosinophils. There is marked dermal edema, with necrosis and fibroblast proliferation. In some cases there is mild hyperkeratosis or superficial ulceration of the overlying epidermis. Trypanosomes have been demonstrated in skin biopsy specimens and touch preparations.⁴⁰ Rare trypomastigotes may be seen multiplying in the interstitium at the inoculation site.

Although several organs may show gross and microscopic changes, these findings are not pathognomonic. Lymph nodes are grossly enlarged. In the early stages of disease there are prominent germinal centers, follicular hyperplasia, sinus histiocytosis, lymphophagocytosis (Fig 3.13), and numerous plasma cells with occasional Russell bodies, which are globules of immunoglobulin (usually IgM) approximately 3 μm in diameter. There may be focal intranodal hemorrhages. In later stages, lymph nodes may shrink, become fibrotic and lymphocyte-depleted, (Fig 3.14) and demonstrate lymphophagocytosis. Cytologic examination of node imprints may show large numbers of organisms. The spleen may be moderately enlarged. Red pulp is congested and white pulp has foci of histiocytic hyperplasia and lymphophagocytosis, areas of necrosis 2 mm to 5 mm in diameter, and occasional giant cells (Figs 3.15 & 3.16).

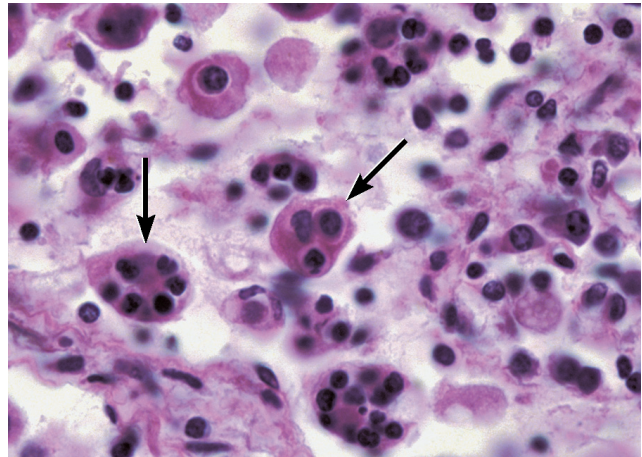


Figure 3.13
Lymphophagocytosis (arrows) in histiocytic infiltrate in lymph node from an 18-year-old Zambian female who died of Rhodesian trypanosomiasis. x700

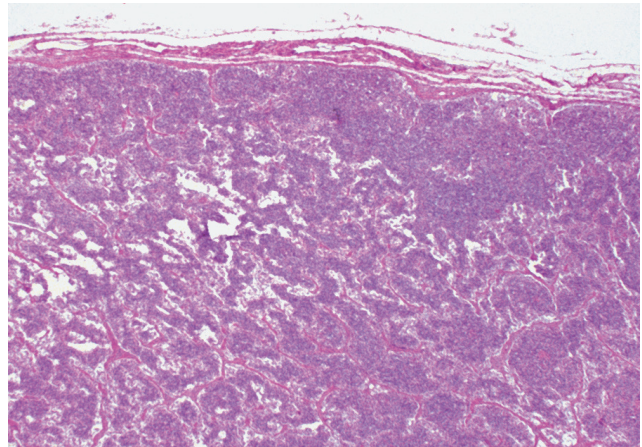


Figure 3.14
Follicular atrophy and histiocytic hyperplasia in lymph node from patient described in Figure 3.13. x15

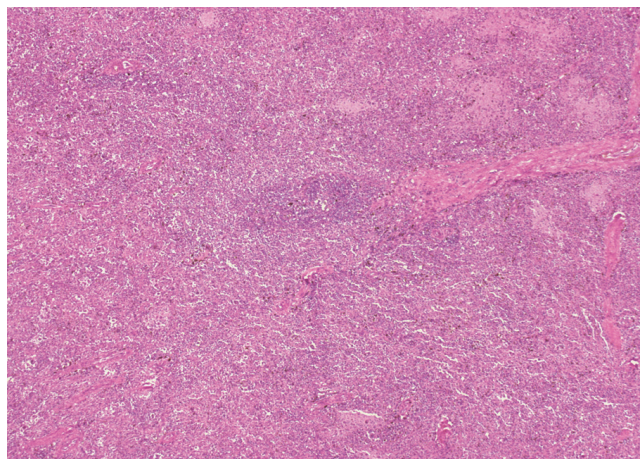


Figure 3.15
Spleen of patient described in Figure 3.13. White pulp is reduced and there is histiocytic hyperplasia. x28

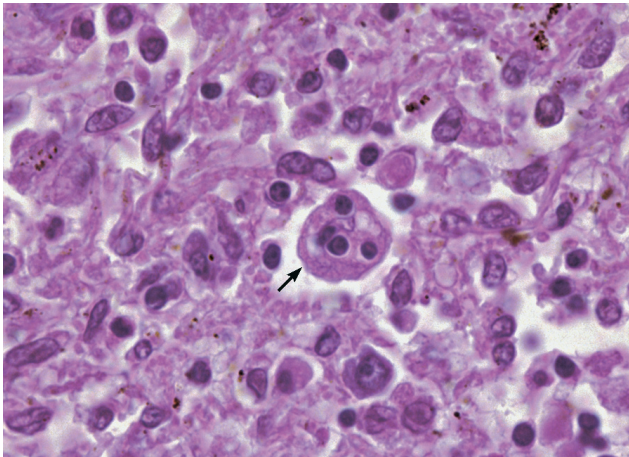


Figure 3.16
Lymphophagocytosis (arrow) in spleen shown in Figure 3.15. x700

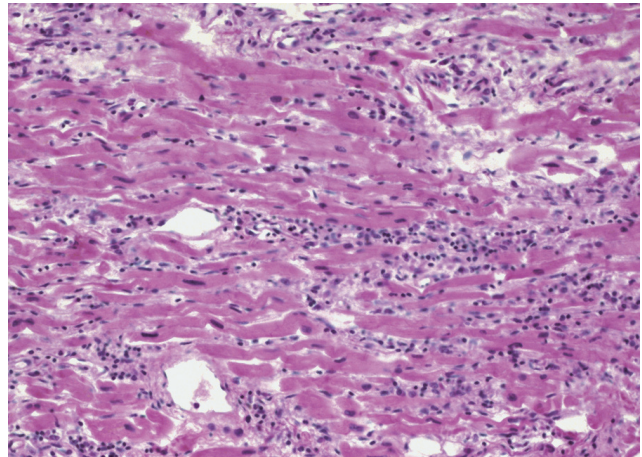


Figure 3.17
Myocarditis in patient described in Figure 3.13. Infiltrating cells are lymphocytes, histiocytes, and plasma cells. There are no eosinophils. Scattered areas of myocytolysis are seen. x140

Although trypanosomes are commonly found in blood, they are rarely seen in tissue sections of any organ.

Cardiac changes, more common in Rhodesian trypanosomiasis, may include pericardial and subendocardial petechiae, thickened valves, endocardial thickening, and mild cardiac enlargement. Histologic sections reveal pancarditis with diffuse or focal infiltrates of lymphocytes, macrophages, and plasma cells, with no eosinophils (Fig 3.17). There may be areas of myocytolysis. In advanced infections, there are often irregular areas of fibrosis in the ventricular myocardium. Small endocardial granulomas with necrotic eosinophilic centers have been reported. Inflammation in the conduction system produces electrocardiographic changes and, at times, terminal cardiac insufficiency.⁴¹ Pulmonary lesions specifically related to trypanosomiasis are not recorded, but at autopsy the lungs frequently show hypostatic pneumonia, a common terminal event in African trypanosomiasis. Pleural and pericardial effusions may contain trypanosomes and lymphocytes.

CNS findings are nonspecific and similar to those of viral encephalitis. The brain may be slightly swollen. Gross findings include perivascular sheathing, hyperemia, occasional ecchymoses, small infarcts,⁴² expansion of the white matter, decrease in ventricular spaces, and evidence of herniation (Figs 3.18 & 3.19). Long-standing meningoencephalitis may result in ventricular dilatation caused by atrophy of the subcortical white matter, and meningeal thickening and opacification.

Microscopically, leptomeninges, Virchow-Robin spaces, and vessel walls are infiltrated by lymphocytes, plasma cells, and macrophages (Figs 3.20 to 3.23).⁴³ The cellular infiltrate typically contains scanty eosinophils. Dürck's nodes, which can be seen in sectioned gross specimens, represent compact lymphohistiocytic perivascular infiltration (Fig 3.24). Two cytologic abnormalities suggest Afri-

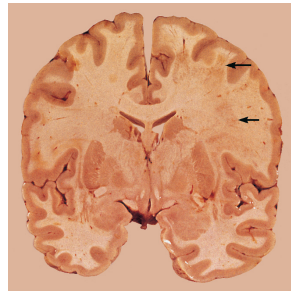


Figure 3.18
Coronal section of brain of Ugandan patient showing congestion of white matter and petechial hemorrhages (arrows).

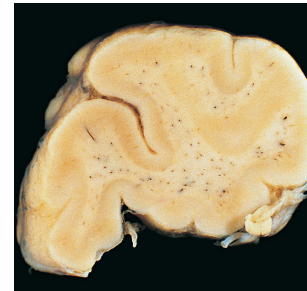


Figure 3.19
Section of cerebral cortex of Zambian patient with Rhodesian trypanosomiasis, showing marked congestion and scattered petechial hemorrhaging in white matter.

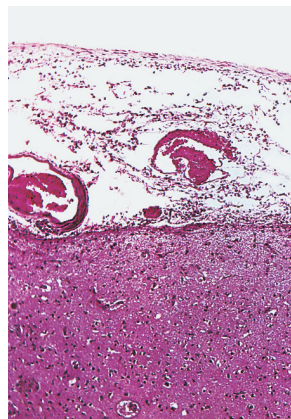


Figure 3.20
Cerebrum in Gambian trypanosomiasis showing congestion, edema, and chronic inflammatory cells in leptomeninges. x70

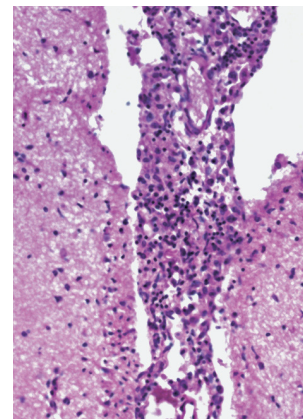


Figure 3.21
Chronic leptomeningitis in Rhodesian trypanosomiasis in patient described in Figure 3.13. Lymphocytes and histiocytes infiltrate the pia and arachnoid. x72

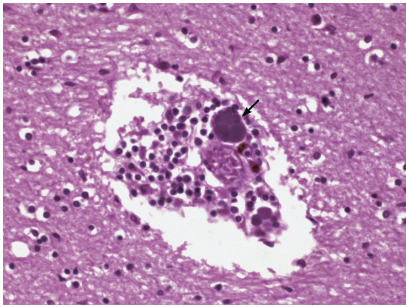


Figure 3.22
Rhodesian trypanosomiasis infection, showing Virchow-Robin space around cerebral blood vessel with lymphohistiocytic perivascular infiltration. Note morular cell (arrow) in infiltrate. x180

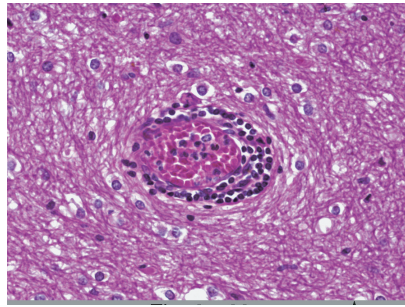


Figure 3.23
Lymphohistiocytic infiltration of Virchow-Robin space surrounding blood vessel (perivascular cuffing) in cerebellum in Rhodesian trypanosomiasis. x180

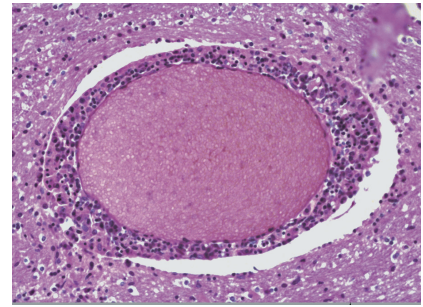


Figure 3.24
Compact lymphohistiocytic perivascular infiltration (often called Dürck's nodes) in brain in Rhodesian trypanosomiasis. x100

can trypanosomiasis, although they are not pathognomonic: lymphophagocytosis and morular Mott cells, which are plasma cells whose cytoplasm is distended up to 20 µm in diameter by Russell bodies (Figs 3.22 & 3.25 to 3.27).⁴⁴ Gliosis, marked by proliferation of microglial rod cells and gemistocytes, is prominent, especially in the superficial cortex, basal ganglia, and brain stem (Figs 3.28 & 3.29). In contrast, demyelination with reactive astrocytosis is minimal, focal, and perivascular. In chronic disease, there is focal hemorrhage and destruction of neurons. Careful examination may very rarely reveal organisms in the Virchow-Robin spaces. Involvement of the brain stem, choroid plexus, spinal cord, cranial nerves, and peripheral nerves have been reported.⁴²

Diagnosis

Early diagnosis reduces the risk of transmission and irreversible neurologic disorders. Clinical diagnosis of

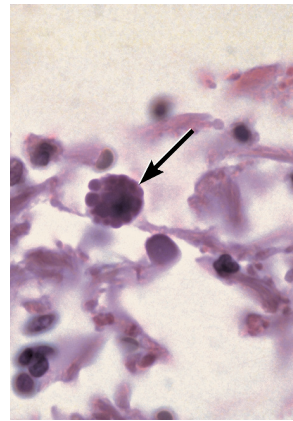


Figure 3.25
Morular cell (arrow) in leptomeninges of 16-year-old female from Burundi who died of Rhodesian trypanosomiasis. Nucleus of original plasma cell is visible in morular cell. x640

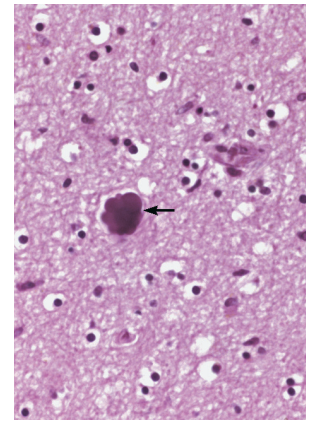


Figure 3.26
Morular cell (arrow) in parenchyma of brain of 35-year-old Congolese male who died of trypanosomiasis. x270

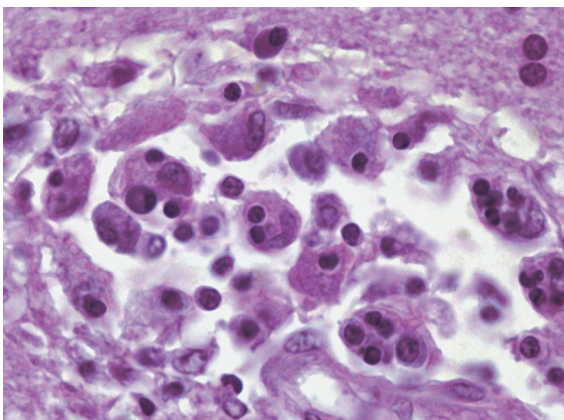


Figure 3.27
Focus of histiocytic infiltrate in brain of patient described in Figure 3.13, demonstrating lymphophagocytosis in Rhodesian trypanosomiasis. x625

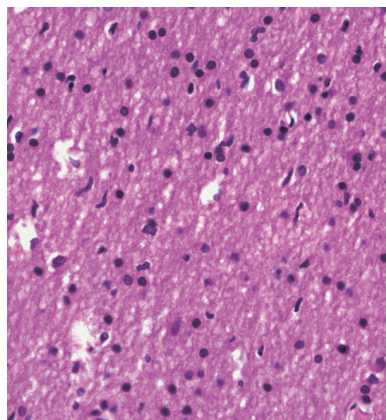


Figure 3.28
Microglial proliferation in brain of patient described in Figure 3.13 with Rhodesian trypanosomiasis. x230

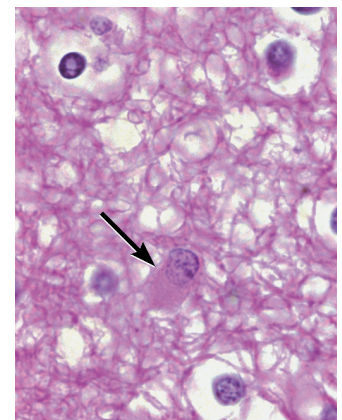


Figure 3.29
Gemistocytic astrocyte (arrow) in Rhodesian trypanosomiasis. Note eccentric nucleus and swollen cell body. x630

African trypanosomiasis is based on symptoms and a history of residence in or travel to an endemic area. The long, asymptomatic first phase of Gambian trypanosomiasis makes early diagnosis difficult. Elevated levels of serum IgM are not considered diagnostic; however, increased IgM titers in CSF, a leukocyte count above 5 cells/mm³, and a total protein level greater than 40 mg/100 ml are highly suggestive of CNS involvement.⁴⁵⁻⁴⁷

Definitive diagnosis depends on microscopic identification of the parasite. In the early stage of disease, diagnosis is confirmed by demonstrating trypanosomes in films of peripheral blood or in aspirates of the chancre, enlarged lymph nodes, or bone marrow. Because the number of parasites in peripheral blood varies cyclically, several blood samples should be taken at various times. Thick and thin blood films should be studied and smears should be fixed and stained with Giemsa (Figs 3.30 & 3.31). Motile trypanosomes can be identified in an unstained wet preparation. Concentration by centrifugation or ultracentrifugation may increase the yield and simplify the search for parasites. Methods used on centrifuged blood samples include examination of the buffy coat, minianion-exchange column, and the quantitative buffy coat (QBC[®]) technique.^{48,49} Giemsa-stained touch preparations of excised lymph nodes may permit early identification of the parasite. In the late stage of disease, organisms may be observed in the sediment of centrifuged CSF. In vitro culture and animal inoculation techniques have had limited use. Antigen detection and DNA assays are being developed.^{46,50,51}

Serologic tests are not clinically useful because of their variable sensitivity and specificity. Cutaneous leishmaniasis or exposure to nonpathogenic trypanosomes may cause false positive serologic findings.⁵² A further limiting factor is that, in Rhodesian trypanosomiasis, seroconversion takes place 2 to 4 weeks after the onset of clinical symptoms. Serologic tests are sometimes useful for epidemiologic surveys or screening for Gambian trypanosomiasis. Tests to determine antibody levels in serum and CSF include the card agglutination trypanosomiasis test (CATT), rapid latex agglutination test, indirect immunofluorescence test, and ELISA.⁵³⁻⁵⁵

Clinical signs and symptoms of African trypanosomiasis must be distinguished from those of reactive arsenical encephalopathy, a complication of treatment with melarsoprol.

Treatment and Prevention

When diagnosed early, African trypanosomiasis has a high cure rate. The type of treatment depends on the phase of disease. Pentamidine isethionate is used to treat the initial phase of Gambian trypanosomiasis and for chemoprophylaxis or early CNS involvement.⁵⁶ Suramin is used for the initial phase of Rhodesian trypanosomiasis. Melarsoprol

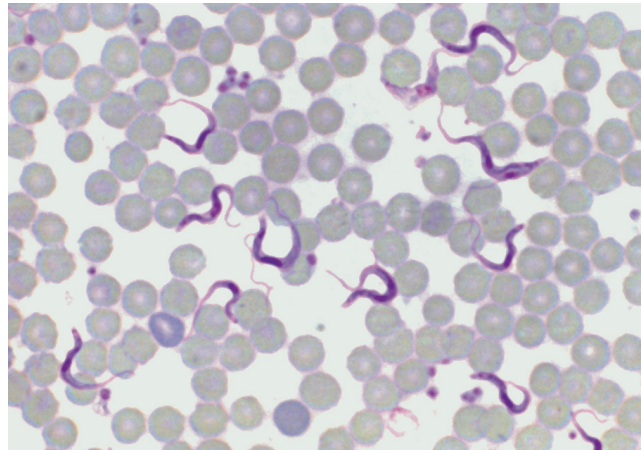


Figure 3.30
Giemsa-stained thin blood film from patient with early Gambian trypanosomiasis, demonstrating heavy parasitemia of trypomastigotes. Giemsa x680

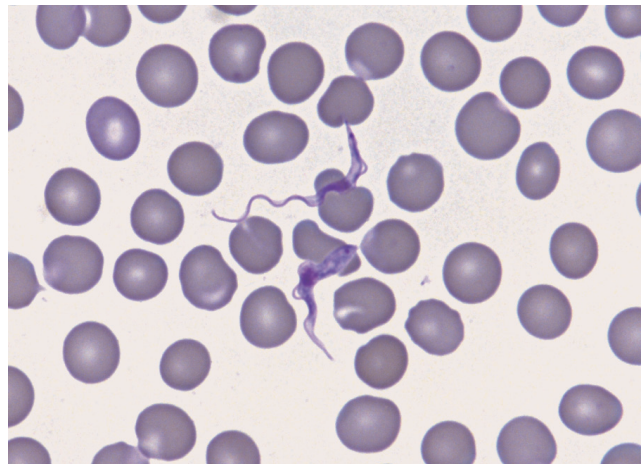


Figure 3.31
Giemsa-stained thin blood film from patient with Rhodesian trypanosomiasis, showing long (upper) and short forms of *Trypanosoma brucei rhodesiense*. Giemsa x990

(Arsobal[®], Mel B[®]), the only available drug that can cross the blood-brain barrier, is used to treat advanced stages of both Gambian and Rhodesian trypanosomiasis. This drug is an arsenical derivative that can have drastic side effects, including seizures associated with acute cerebral edema, rapidly progressive coma without seizures, or acute nonlethal mental disturbances without neurological signs. Reactive arsenical encephalopathy, characterized by acute vasculitis, can occur in either the hemolympathic or meningoencephalitic stage and is fatal in up to 38% of patients.^{43,57} In parts of Central Africa nearly one third of patients are infected with parasites that are resistant to melarsoprol. For Gambian trypanosomiasis, eflornithine (DMFO, Ornidyl[®]) administered orally or intravenously for 14 days is more effective and has fewer adverse effects than other medications.⁵⁸ Nifurtimox – eflornithine in combination has been proposed as an effective regimen for second-stage *Trypanosoma brucei*

gambiense.⁵⁹ The pharmaceutical industry had suspended production of eflornithine for commercial reasons, but through a cooperative effort between public and private entities, the drug is once again available for distribution in endemic countries.⁶⁰ Nifurtimox (Lampit®) is effective against arsenical-resistant Gambian trypanosomiasis.³⁴

There is no available vaccine against African trypanosomiasis.⁶¹ Besides vector control, the only preventive measure is to avoid tsetse-fly bites, bearing in mind that the flies feed during the day, are unaffected by insect repellents, and can bite through lightweight clothing.

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Acknowledgements

Figure 3.3
Specimen contributed by LA Rosati

Figure 3.4
Specimen contributed by LA Rosati

Figure 3.6
Specimen contributed by LA Rosati

Figure 3.9
Clay-Adams Medichrome Series

Figure 3.10
Contributed by Richard P Strong

Figure 3.11
National Museum of Health and Medicine #02-0668

Figure 3.12
National Museum of Health and Medicine #54-13845

Figure 3.14
Specimen contributed by R Purohit

Figure 3.30
Specimen contributed by LR Ash

Figure 3.31
Specimen contributed by LA Rosati