8.8.12 Chagas disease 1459

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8.8.12 Chagas disease 1459 New drug candidates Fexinidazole, a 5-nitroimidazole, was rediscovered by the Drugs for Neglected Diseases initiative (DNDi) after having reviewed over 700 nitroheterocyclic compounds. The molecule was able to cure mouse models of infection after oral dosing and to cross the blood-brain barrier. Fexinidazole is rapidly metabolized to a sulf- oxide and a sulfone, both metabolites are trypanocidal, and reach significant plasma levels. Phase I clinical studies were completed successfully demonstrating the safety of a 10-day oral treatment regime. Phase II/III clinical trials are almost completed. Several hundred patients with stage II disease were treated and all cleared parasitaemia after treatment, the 2-year follow-up is still ongoing. There is hope that the new drug will be on the market and freely available by 2019. A second clinical candidate is the benzoxaborole SCYX-7158 which is also in the portfolio of DNDi. This novel class of boron- containing molecules is orally bioavailable and able to pass the blood-brain barrier. SCYX-7158 completed phase I clinical studies successfully. The long terminal half-life gives hope for a short treat- ment course, maybe even single dose treatment. Phase II/III trials are in progress. Prevention/Individual protection A vaccine for sleeping sickness is not available and chemo-prophylaxis is not recommended because of the toxicity of the available drugs and the low risk of infection. Travellers should take notice of the risk of sleeping sickness, be informed on the transmission and clinical presentation of the disease and preven- tion. The only preventive measure is the protection from tsetse fly bites. The flies are attracted to bright or contrasting colours, particularly blue, as well as to the dust and motion of vehicles. As routine preventive measures, travellers should avoid known areas of tsetse flies, travel in endemic foci in cars with screened or closed windows, use insect repellent, and wear wrist- and ankle- length clothes. Efforts to eliminate HAT The first milestone in the effort to eliminate HAT was the London Declaration on Neglected Tropical Diseases launched in 2012. It set the goal to eliminate HAT and four other neglected dis- eases by the year 2020 (i.e. reduce the number of reported cases <2000/year and the number of active foci). In 2014 WHO estab- lished a Coordination Network for HAT to strengthen efforts to eliminate the disease. Stakeholders are national sleeping sickness control programmes, organizations developing drugs and diagnos- tics, governmental organizations, NGOs, and philanthropic organ- izations. New diagnostics and drugs are prerequisites for elimination especially an oral drug for both disease stages, rendering staging unnecessary. Another important element in the elimination effort is vector control which is based on new types of targets, attractants, sterile male flies, or on the treatment of domestic animals which the flies feed on. Elimination is certainly a realistic goal provided the new tools become available. FURTHER READING Balmer O, et al. (2011). Phylogeography and taxonomy of Trypanosoma brucei. PLoS Negl Trop Dis, 5, e961. Blum JA, et al. (2008). Cardiac involvement in African and American

trypanosomiasis. Lancet Infect Dis, 8, 631–41. Brun R, et al. (2010). Human African trypanosomiasis. Lancet, 375, 148–59. Eperon G, et al. (2014). Treatment options for second-stage gambiense human African trypanosomiasis. Expert Rev Anti Infect Ther, 12, 1407–17. Franco JR, et al. (2014). The journey towards elimination of gambiense human African trypanosomiasis: not far, nor easy. Parasitology, 141, 748–60. Kennedy PGE (2013). Clinical features, diagnosis, and treatment of human African trypanosomiasis (sleeping sickness). Lancet Neurol, 12, 186–94. Kuepfer I, et al. (2011). Clinical presentation of T.b. rhodesiense sleeping sickness in second stage patients from Tanzania and Uganda. PLoS Negl Trop Dis, 5, e968. Mäser P, et al. (2012). Antiparasitic agents: new drugs on the horizon. Curr Opin Pharmacol, 12, 562–6. Mesu VKBK, et al. (2018). Oral fexinidazole for late-stage African Trypanosoma brucei gambiense trypanosomiasis: a pivotal multi centre, randomised, non-inferiority trial. Lancet, 391, 144–54. Schmid C, et al. (2012). In-hospital safety in field conditions of nifurtimox eflornithine combination therapy (NECT) for T.b. gam biense sleeping sickness. PLoS Negl Trop Dis, 6, e1920. Simarro PP, et al. (2015). Monitoring the progress towards the elim- ination of Gambiense human African trypanosomiasis. PLoS Negl Trop Dis, 9, e3785. Steinmann P, et al. (2015). Contemporary and emerging strategies for eliminating human African trypanosomiasis due to Trypanosoma brucei gambiense: review. Trop Med Int Health, 20, 707–18. Vale GA, Torr S (2004). Development of bait technology to control tsetse. In: Maudlin I, Holmes PH, Miles MA (eds). The trypanoso miases, pp. 509–24. CABI, Wallingford. Welburn SC, et al. (2016). Beyond Tsetse—Implications for Research and Control of Human African Trypanosomiasis Epidemics. Trends Parasitol, 32, 230–41. World Health Organization (2013). Control and surveillance of African trypanosomiasis. WHO Technical Report Series 984. WHO, Geneva. 8.8.12 Chagas disease Michael A. Miles A poeira de Curvelo não az mal para ninguém não Do pulmão lá ninguém morre O que mata é o coração The dust of Curvelo does not harm anybody No one dies there of lung disease What kills is the heart (From the poem O galo cantou na serra by Luiz Claudio and Guimarães Rosa)

section 8 Infectious diseases 1460 ESSENTIALS Trypanosoma cruzi, the protozoan parasite that causes Chagas dis- ease, is a zoonotic infection with many mammal host and vector species. It is transmitted to humans by contamination of mucous membranes or abraded skin with infected faeces of bloodsucking triatomine bugs, also by blood transfusion, organ transplantation, transplacentally, and orally by food contaminated with infective forms. It multiplies intracellularly (pseudocysts) as amastigotes in a wide range of mammalian cells, particularly heart and smooth muscle, from which flagellated trypomastigotes emerge to reinvade cells or circulate in blood. Around 7 million people are infected in Latin America; imported cases and congenital cases occur elsewhere. Clinical features There are classically two principal phases. (1) Acute—asymptomatic or with manifestations that can include fever, myalgia, headache, vomiting, diarrhoea, anorexia, facial or generalized oedema, rash, generalized lymphadenopathy, and hepatosplenomegaly; there may be a lesion at the portal of entry; the acute phase is fatal in less than 10% of cases.
(2) Chronic—indeterminate (asymptomatic) or, in up to 30% of those recovering from the acute phase, with cardiac in- volvement (typically cardiomyopathy leading to congestive cardiac failure, arrhythmias and ECG abnormalities due to focal inflamma- tory lesions of the conducting system), also megaoesophagus and megacolon. Infection is opportunistic, relapsing in the immunocom- promised. Meningoencephalitic involvement may occur in the im- munocompromised (most typically with HIV/AIDS), and is also seen in congenital cases. Diagnosis (1) Acute phase—parasitaemia is scanty, but circulating trypomastigotes may be detectable in the acute phase by microscopy of blood, en- hanced by concentration methods. (2) Chronic phase—multiple

cultures of centrifuged (plasma de- pleted) blood or feeding and subsequent dissection of laboratory- reared triatomines (xenodiagnosis) may reveal infection. (3) Serological testing—can demonstrate evidence of infection, but needs to be standardized with reference sera and by external quality control. Treatment (1) Acute phase—proven cases should be treated promptly with benznidazole or nifurtimox, but there is no guarantee that a full course of treatment will eliminate the infection. (2) Chronic phase—the value of drug treatment for adults in the chronic phase is still debated; supportive care may include the following (a) for heart disease—conventional drug treatment for cardiac failure and arrhythmias; cardiac pacemaker; (b) for megaoesophagus—dilatation; segmentary removal of stomach muscle; replacement of the distal oesophagus; (c) megacolon— resection and anastomosis with the rectal stump. Prevention Proven methods of controlling domestic triatomine bugs include insecticide spraying (with pyrethroids), health education, commu- nity support, and house improvement. Serological surveillance of children detects residual endemic foci or congenital transmission and is vital for monitoring the success of control programmes.

The Southern Cone programme against Triatoma infestans is con- sidered a model for international cooperation in disease control. There is no vaccine. Introduction and aetiology In 1907, in the space of a few months, the Brazilian scientist Carlos Chagas discovered the disease that bears his name and described the entire life cycle of the causative organism. Chagas first found the protozoan agent Trypanosoma cruzi in the gut of the large blood- sucking insect vector, the triatomine bug (order Hemiptera, family Reduviidae, subfamily Triatominae) (Fig. 8.8.12.1). Later he re- turned to bug-infested houses and detected T. cruzi in the blood of sick children. T. cruzi is a kinetoplastid protozoan. In addition to the nucleus, it has a second, microscopically visible DNA-containing organelle, the kinetoplast. The main life cycle stages (trypomastigote, amastigote, epimastigote) are distinguished by the position of the kinetoplast relative to the nucleus and by the presence or absence of a free flagellum. Vector-borne transmission of T. cruzi is by contamination of the mammal host with infected faeces of triatomine bugs, not by their bite. During or shortly after feeding, bugs release blackish liquid faeces and urine on to the skin of the host. Infective forms (metacyclic trypomastigotes) penetrate mucous membranes or abraded skin. Inside the mammal, T. cruzi is primarily an intracellular para- site. Trypomastigotes enter nonphagocytic or phagocytic cells, in which they transform to ovoid or round aflagellate amastigotes that Fig. 8.8.12.1 Adult female triatomine bug (Panstrongylus megistus), with a single egg shown adjacent to the tip of the abdomen. Courtesy of Dr T. V. Barrett.

 multiply inside the cytoplasm of the cell by binary fission to produce a pseudocyst (Fig. 8.8.12.2). After 5 days or more, the pseudocyst ruptures to release numerous new trypomastigotes, which reinvade cells or circulate in the blood. Multiplication may occur at the site of infection. Pseudocysts may occur in a wide range of cell types but subsequently predominate in muscle, especially heart and smooth muscle. In the blood, trypomastigotes are small, often C-shaped, with a large terminal kinetoplast (Fig. 8.8.12.3). In fulminating or experimental infections, slender highly motile trypomastigotes may also sometimes be seen. Trypomastigotes do not multiply in the blood. Triatomine bugs become infected by taking a blood meal from an infected mammal; birds and reptiles are not susceptible to infection. Infection in the bug is confined to the alimentary tract, where T. cruzi multiplies by binary fission as epimastigotes (kineto- plast adjacent to the nucleus). Metacyclic trypomastigotes are pro- duced in the hindgut and rectum of the bug. All stages of the T. cruzi life cycle can be cultured in vitro. T. cruzi can also be transmitted by blood transfusion and organ transplantation, across the placenta, via breast milk (rarely), and orally

through food contaminated by triatomine faeces and the raw meat of infected mammals. Sexual transmission has not been documented. Epidemiology Vector-borne T. cruzi infection is confined to the Americas. Closely related organisms of the same subgenus (Schizotrypanum) are cosmopolitan in bats. The vast majority of more than 140 recognized triatomine bug species are restricted to the Americas. Their natural habitats are the refuges of mammals, birds, and reptiles, in trees, in burrows, and among rocks. All mammals are thought to be suscep- tible to T. cruzi, which has been reported from at least 150 mammal species. The opossum (Didelphis spp.) is the most commonly re- ported sylvatic host. A few triatomine species thrive as domestic colonies. More than 10 000 bugs have been found in a single house. Before the recent Southern Cone initiative to control Triatoma infestans, this vector species was widespread in rural housing of the Southern Cone countries of South America (Argentina, Bolivia, Brazil, Chile, Paraguay, Uruguay, and southern Peru). Rhodnius pro lixus is the common vector in northern South America and has also been an important vector in Central America, with Triatoma dim idiata as secondary vector in the same regions. Panstrongylus meg istus (Fig. 8.8.12.1) infests central and eastern Brazil, and Triatoma brasiliensis north-eastern Brazil. Animals that share human dwell- ings, such as guinea pigs, dogs, cats, rats, and mice are domestic res- ervoirs of T. cruzi infection. Chickens, although not susceptible to T. cruzi, encourage triatomine infestation and can sustain large bug colonies. Serological surveys suggest that 6–7 million people may still be infected with T. cruzi in South and Central America, a level that has been reduced from up to 20 million around four decades ago. In some communities, seropositivity rates may still exceed 50%. As expected from the precarious contaminative route of trans- mission, prevalence rises with age. Based on prevalence, before recent control initiatives, it was estimated that up to 300 000 new infections might occur in Latin America each year; this is now reduced to less than 60 000/year. Only approximately 1500 cases are known from the Amazon basin, about half of these due to oral transmission by drinking plant juices contaminated by live triatomine bugs during juice extraction or storage (e.g. juice from berries of açaí or bacaba palms or sugar cane). Oral outbreaks also occur elsewhere; one among schoolchildren in Caracas, Venezuela, due to guava juice, involved 103 cases. There are rela- tively few Amazonian cases because the local forest vectors do not colonize houses. For the same reason, autochthonous vector- borne infection is very rare in the United States of America. However, there is an autochthonous cycle of T. cruzi infection among dogs in Texas. Abundant local vectors (Triatoma species) and established sylvatic transmission cycles, involving mammals such as opossums, racoons and woodrats, are widespread in the United States. Not surprisingly, sporadic T. cruzi infections can be found among migrants from Latin America. Serological studies indicate that there may be up to 300 000 carriers of T. cruzi infection in the United States among migrants, and that universal surveillance of blood donors should, therefore, be introduced. It is estimated (a) (b) Fig. 8.8.12.2 Pseudocyst of Trypanosoma cruzi. Pseudocyst in (a) heart muscle and (b) umbilical cord, from a congenital case of Chagas disease. (a) Courtesy of J E Williams; (b) courtesy of Dr Hipolito de Almeida. Fig. 8.8.12.3 Trypanosoma cruzi C-shaped trypomastigote in blood. Note the large posterior kinetoplast.

 that there are more than 100 000 carriers of infection in Europe. Cases of transmission by blood or organ donors and rare con- genital cases can thus occur worldwide. In 2007, the World Health Organization (WHO) launched a ‘Global Network for Chagas Elimination’ to raise global awareness and coordinate prevention of transmission. Initial acute infections are frequently asymptomatic or over- looked. It is thought that less than 10% of acute infections in chil- dren or young adults are fatal. Morbidity due to Chagas disease arises primarily

from the chronic infection. Once acquired, infec- tion is usually carried for life. Around 30% of those infected will subsequently display ECG abnormalities and chagasic cardiomy- opathy, and a proportion of those have associated megaoesophagus or megacolon. There are regional differences in the epidemiology of Chagas disease. Research in molecular genetics has shown that the species T. cruzi is remarkably diverse genetically. Six distinct genetic lineages are currently described, TcI-TcVI. The six lineages have complex disparate but partially overlapping geographical and ecological distributions and are circumstantially associated with the different epidemiological features. TcI is the principal agent north of the Amazon, in association with chagasic heart disease but where gastrointestinal involvement, megaoesophagus, and megacolon are considered to be rare. TcII is one of three principal agents of Chagas disease in the Southern Cone region of South America, where chagasic cardiomyopathy, megaoesophagus, and megacolon are found. TcIII is seldom isolated from humans but is widely distributed with the natural armadillo host Dasypus nove mcinctus. TcIV is a sporadic secondary agent of Chagas disease in Venezuela. TcV and TcVI, like TcII, are also agents of Chagas dis- ease in the Southern Cone region, and are known to be relatively recent hybrids of TcII and TcIII. Pathogenesis and pathology At the portal of entry, local multiplication of T. cruzi may lead to uni- lateral conjunctivitis or to a skin lesion (Fig. 8.8.12.4). Unruptured pseudocysts in muscle apparently generate no inflammatory re- sponse. Pseudocyst rupture is followed by infiltration of lympho- cytes, monocytes, and/or polymorphonuclear cells. Antigens released from pseudocysts may spread and be adsorbed on to ad- jacent uninfected cells. Such uninfected cells may be attacked by the immune response of the host and be destroyed. In this way, expanded focal lesions may be produced. Post-mortem histology of human hearts and experimental studies in dogs have demon- strated a clear association between ECG abnormalities and focal lesions in the conducting system of the heart. Much damage may occur in the acute phase of infection, particularly if pseudocysts are numerous. Post-mortem histology has demonstrated that neuron loss is a feature of chagasic cardiopathy and of megasyndromes, which may be exacerbated by further disease or age-related loss. Thus, a threshold may be reached, often many years after the acute infection, at which organ function is perturbed. Further ECG abnormalities, aperistalsis, and organ enlargement may ensue. This ‘neurogenic’ pathogenesis has been linked to sudden death. It is proposed that pathological exposure of normal host- sequestered antigens, or sharing of antigens between T. cruzi and its host, may precipitate autoimmune pathogenesis. Some chronic chagasic cardiomyopathy is said to display a renewed intense inflammatory response and a progressive diffuse myocarditis, and a slow decline in cardiac function. The contribution of the lifelong infection to the pathogenesis of chronic Chagas disease continues to be controversial. Although some studies have suggested that elimination of residual infection improves prognosis a recent randomized study (BENEFIT) treat- ment of 2854 patients already with some chagasic cardiomyop- athy showed no reduction in cardiac clinical deterioration during five years of follow-up, despite evidence of reduced parasitaemias; asymptomatic trials are desirable. After the initial acute phase, trypomastigotes are detectable in the blood only by sensitive in- direct methods such as polymerase chain reaction (PCR). Similarly, pseudocysts in the tissues are infrequent, but are detectable im- munologically and by amplification of T. cruzi DNA. In vivo imaging of mice with prolonged chronic infections of bioluminescent trans- genic T. cruzi has revealed the presence of cryptic, dynamic, wide- spread, and unpredictably distributed foci of parasite replication. Severity of T. cruzi infection is considered to be influenced by the balance between the Th1 (cell mediated) and Th2 (antibody) arms of the immune response and the extent of the inflammatory response, the indeterminate form being associated with an anti-inflamma- tory cytokine profile. Patients immunocompromised by AIDS have impaired Th1 responses. Thus, HIV-

positive patients chronically infected with T. cruzi may suffer reactivation of the acute phase of Chagas disease, with microscopically patent parasitaemia, poor prognosis, and risk of meningoencephalitic invasive lesions. At the level of gross pathology, substantial megacardia may be seen. Thinning of the myocardium may be present, with focal an- eurysms visible upon transillumination, especially at the apex of the left ventricle (Fig. 8.8.12.5) and thrombus in the right atrial appendage (Fig. 8.8.12.6). Apical aneurysm is considered to Fig. 8.8.12.4 Romaña's sign in acute Chagas disease.

8.8.12 Chagas disease 1463 be a pathognomonic sign of chronic chagasic cardiomyopathy. Megaoesophagus (Fig. 8.8.12.7) and megacolon (Fig. 8.8.12.8) may show enormous dilatation and thinning of the wall. Chagasic megaoesophagus is more frequent than chagasic megacolon, but both may occur in the same patient and are often accompanied by chagasic heart disease. Chagasic megaoesophagus may be a prelude to carcinoma. Occasionally megasyndromes may arise in infants, following congenital infection. Clinical features Classically, there are two principal clinical phases of Chagas dis- ease. In the acute phase, symptoms can include fever, myalgia, head- ache, hepatosplenomegaly, lymphadenopathy, facial or generalized oedema, rash, vomiting, diarrhoea, and anorexia. If T. cruzi invasion has been via the conjunctiva, Romaña's sign might be present: uni- lateral conjunctivitis, chemosis, and periophthalmic oedema (Fig. 8.8.12.4). If the portal of entry is the skin, an indurated oedema- tous cutaneous lesion (chagoma) may be seen. Regional lymph- adenopathy may be present. Multiple chagomas occasionally occur in acute-phase infections in infants or in reactivated immunocom- promised cases. ECG abnormalities include sinus tachycardia, in- creased PR interval, T-wave changes, and low QRS voltage. The incubation period can be as short as 2 weeks or as long as several months if infection is due to transfusion of contaminated blood. General lymphadenopathy and splenomegaly are frequent in blood transfusion-acquired infections. Fig. 8.8.12.5 Apical aneurysm of the left ventricle in chronic Chagas disease. Courtesy of Dr J. S. de Oliveira. Fig. 8.8.12.6 Mural thrombus filling the right atrial appendage. Copyright D. A. Warrell. Fig. 8.8.12.7 Megaoesophagus seen by radiography in chronic Chagas disease. Courtesy of Dr J. S. de Oliveira. Fig. 8.8.12.8 Megacolon post-mortem in chronic Chagas disease. Courtesy of Dr J. S. de Oliveira.

section 8 Infectious diseases 1464 Congenital acute infection may cause fever, oedema, metastatic chagomas, neurological signs such as convulsions, tremors, and weak reflexes, and apnoea. Hepatosplenomegaly is frequent. The ECG is usually normal but low-voltage complexes, reduced T-wave height, and longer atrioventricular (AV) conduction time may be present. Meningoencephalitis is rare in adults, more frequent in infants, and common in immunocompromised patients. It carries a poor prognosis. The clinical picture of AIDS-associated chagasic meningoenceph- alitis may be similar to toxoplasmosis. Haemorrhagic necrotic en- cephalitis is described in the nests of trypanosomes in microglia. Congenital infection may resemble toxoplasmosis, cytomegalovirus infection, or syphilis, with an increased likelihood of abortion and premature birth. Congenital infection is well known in Bolivia but less frequently reported from Venezuela and Brazil. The symptomatic or asymptomatic acute phase infection is followed by the chronic phase, which may be symptom-free (indeterminate) for life. However, symptoms emerge in up to 30% of patients recovering from the acute phase. Cardiac symptoms include arrhythmias, pal- pitations, chest pain, oedema, dizziness, syncope, and dyspnoea. The cardiac enlargement may be massive with chronic congestive cardiac failure, apical aneurysm (Fig. 8.8.12.5), and thrombus in the right atrial appendage (Fig. 8.8.12.6). The cardiac conducting

system is in- volved, especially the sinus node, bundle of His and AV node, in which there is mononuclear and mast-cell infiltration, inflammation, and fibrosis. Characteristic ECG abnormalities are right bundle branch block (RBBB) and left anterior hemiblock (LAH). AV conduction abnormalities, including AV block, may be present. Arrhythmias may include sinus bradycardia, sinoatrial block, ventricular tachycardia, primary T-wave changes, and abnormal Q-waves. The severity of heart disease is graded by the degree of disturbance; there are several alter- native published scales of severity. Sudden death is attributable, not to ruptured aneurysm, but to arrhythmias often precipitated by exercise (e.g. on the football field). Radiography may reveal megacardia (Fig. 8.8.12.9). Signs of oesophageal involvement include loss of peristalsis, regurgitation, and dysphagia (Fig. 8.8.12.7). Parotid enlargement may be associated. In megacolon, there may be failure of defaecation, constipa- tion, and faecaloma (Fig. 8.8.12.8). Progressive dilatation of either the oesophagus or colon can be graded clinically according to severity and may be detectable by radiography. Megaduodenum and megaureter are also described. The lymph nodes between the pul- monary trunk and the aorta are frequently enlarged. The differential diagnosis includes other types of heart disease and causes of ECG abnormalities. RBBB and LAH are indicative, but a history of exposure to T. cruzi infection and laboratory diagnostic evidence must be considered (see next). Laboratory diagnosis A history of exposure to triatomine bugs, to transfused blood that is potentially contaminated or a prolonged stay in endemic regions must be considered. Rarely short-term visitors to endemic regions may acquire infection. In the acute phase motile trypomastigotes might be seen in unstained, wet blood preparations examined by microscopy (Fig. 8.8.12.3). Nevertheless, parasitaemia is often scanty or undetectable by this method. The sensitivity of parasitological diagnosis may be enhanced by microscopy of samples prepared with concentration methods, such as the centrifugation pellet from separated serum (Strout’s method), the haematocrit buffy coat layer, Giemsa-stained thick films, or the centrifugation sediment after lysis of red blood cells with 0.87% am- monium chloride. All these tests may be negative if parasitaemia is low. Potentially infected blood must be handled with care, especially during haematocrit centrifugation, as a single trypomastigote can cause infec- tion. Multiple blood cultures may also be performed, with a sensitive blood agar-based medium and physiological saline overlay. However, before culture the blood cells and potential trypanosomes must be pel- leted by centrifugation and the plasma removed, because antibodies in plasma can lyse the culture form (epimastigote) stage. Even more sensitive than blood culture is xenodiagnosis, in which hungry fourth or fifth instar bugs from a clean triatomine colony, raised from bug eggs and fed only on birds, are allowed to feed on the patient. Bugs are applied in a plastic pot contained discretely in a black bag, which is tied beneath the patient’s forearm. The bugs are dissected 20–25 days later. The hindgut and rectum are drawn out into a drop of sterile physio- logical saline, mixed with a blunt instrument (microspatula), and ob- served microscopically for motile epimastigotes and trypomastigotes. Dissection should be performed behind a small, perspex safety screen or in a microbiological safety cabinet. R. prolixus is the most avid feeder for xenodiagnosis but may cause delayed hypersensitivity reactions in sensitized patients. Anaphylaxis is rare but two cases are known. The local vector should be used as the susceptibility of triatomine species varies with the strain of T. cruzi. If pericardial effusion is a feature of acute infection and the fluid is drained it should be examined by microscopy for the presence of trypanosomes, which might be detectable even if blood parasit- aemia is subpatent. After the acute-phase infection, all the aforementioned methods of parasitological diagnosis will fail except xenodiagnosis and, possibly, multiple blood cultures. Up to 50% of patients in the chronic phase may yield a positive xenodiagnosis, providing at least 10 triatomine bugs are used. Polymerase chain reaction or loop-

mediated iso- thermal amplification (LAMP) of multicopy T. cruzi DNA targets may be sensitive and specific but are not yet available as routine diag- nostic tests. Serum antibody is produced within a few days of T. cruzi Fig. 8.8.12.9 Chest radiograph showing gross cardiac enlargement in a Brazilian woman with chronic Chagas disease. Copyright D. A. Warrell.

8.8.12 Chagas disease 1465 infection and persists for life in untreated patients. There is an early IgM response, but it is not sustained at the high levels seen in African trypanosomiasis. Persistent IgG may be detected by the enzyme- linked immunosorbent assay, the indirect fluorescent-antibody test or the indirect haemagglutination test. Cross reactions may occur with visceral and mucocutaneous leishmaniasis, with treponematoses, and possibly with other hyperimmune responses or autoimmune diseases. Recombinant antigens have been used to improve species specificity and several commercial kits and rapid tests are available, with differing sensitivities, specificities, ease of use, and costs. Most diagnostic kits are prepared from TcII or TcVI antigen preparations; sensitivity of serological diagnosis has been reported to be lower in TcI endemic regions. Quality of commercial tests should not be presumed without reference to authoritative comparative studies. Serological assays must be standardized with negative and positive control sera and by reference to experienced external reference centres to check reprodu- cibility. Transplacentally acquired IgG may persist for up to 9 months in infants born of seropositive mothers. IgM-specific seropositivity in such infants might be an indicator of congenital infection but is not definitive. IgM may decline rapidly in filter paper blood spots if they are used as the source of serum. Serology may be performed post- mortem using pericardial fluid. After early successful treatment of acute cases seropositivity may revert to negative within months; however, treated chronic cases may remain seropositive for decades. There is as yet no definitive biomarker for cure of infection, although PCR with blood samples is considered to be currently the most informative method, parasites, and different T. cruzi genetic lineages, may be sequestered in the tis- sues and undetectable. Treatment Proven acute cases must be treated promptly as it may be life-saving, and in an effort to minimize tissue damage and neuron loss. The syn- thetic oral nitrofuran, nifurtimox was the first successful drug for the treatment of Chagas disease. However, the oral nitroimidazole, benznidazole is now considered to be the first line drug of choice due to fewer side effects. The adult dosage of benznidazole is 5–7 mg/kg in two divided doses for 60 days; for children, 7–10 mg/kg also in two divided doses for 60 days. Adverse effects may demand inter- ruption of treatment. These include rashes, fever, nausea, peripheral polyneuritis, leukopenia, and, rarely, agranulocytosis. Rare cases of Steven’s Johnson syndrome have been reported. Double or even higher doses have been used for immunocompromised patients, es- pecially if meningoencephalitis is present. Nifurtimox for adults is given in three divided daily doses at 8–10 mg/kg for 90 days, up to double doses for infected children. Adverse effects, which may lead to interruption of treatment, can include anorexia, loss of weight, psychological disturbances, excitability, nausea, and vomiting. Up to 40% of adult patients may fail to complete treatment with ei- ther drug, particularly if severe dermatological side effects arise within the first two weeks of treatment. There is no guarantee that a full course of treatment will eliminate the infection. Although the value of drug treatment for chronic infections is still debated, it is favoured for infants, for children under 12 years or by some author- ities for young adults under 15 or 18 years, because children tolerate treatment much better than adults. If not already available locally, favourable access to these drugs may be obtained via WHO; pedi- atric doses are available. As mentioned, there is as yet no definitive diagnostic biomarker of cure of infection after drug treatment. It has been argued that the chronic phase should treated more ag- gressively to

eliminate T. cruzi and so prevent newly emergent in- flammatory foci, further cardiomyopathy and megasyndromes and reduce cardiac block and arrhythmia, and that not only children and recently infected cases but all cases of the indeterminate chronic form of Chagas disease, including chronic chagasic cardiomyopathy grade II of the New York Heart Association classification should be treated unless this is contraindicated by concomitant diseases or pregnancy. Nevertheless, as mentioned, the BENEFIT treatment trial, for patients who already display some chagasic cardiomyop- athy, showed no reduction in the progression of cardiac disease. Posoconazole and ravuconazole, inhibitors of ergosterol me- tabolism, were proposed as promising new drugs for treatment of T. cruzi infection. However, both drugs have failed in clinical trials and in highly sensitive mouse models using bioluminescent trans- genic T. cruzi and in vivo imaging. In acute-phase heart failure, sodium intake is restricted, and di- uretics and digitalis may be indicated. Meningoencephalitis may re- quire anticonvulsants, sedatives, and intravenous mannitol. Heart failure due to Chagas disease may require vasodilatation (angio- tensin-converting enzyme inhibitors) and maintenance of normal serum potassium levels; digitalis is a last resort because it may ag- gravate arrhythmias. A pacemaker may be fitted to improve brady- cardia not responding to atropine, or for atrial fibrillation with a slow ventricular response that is not responsive to vagolytic drugs, or for complete AV block. Amiodarone has been suggested as the most useful drug to treat arrhythmias, but it may still be aggravating. For ventricular extrasystoles lidocaine, mexiletine, propafenone, flecainide, and β-adrenoreceptor antagonists may be effective. Lidocaine may be used intravenously in emergencies. It is essential to consult detailed WHO expert reports and physicians with sub- stantial experience in the management of chagasic heart disease. Surgery is a vital part of case management for Chagas dis- ease. Resection of ventricular aneurysms has been suggested. Specialized surgery has been developed in Brazil for the treatment of megaoesophagus and megacolon. Early megaoesophagus may respond to balloon dilatation. The Heller–Vasconcelos operation, in which a portion of muscle at the junction of the oesophagus and stomach is removed, may alleviate megaoesophagus. Severe megaoesophagus requires replacement of the distal oesophagus (e.g. with a portion of jejenum). The modified Duhamel–Haddad oper- ation has been considered the most successful surgery for correc- tion of a megacolon: after resection, the colon is lowered through the retrorectal stump as a perineal colostomy. Subsequent suturing, under peridural anaesthesia, gives a wide junction between the colon and the rectal stump. Prognosis, even in treated patients who show serological rever- sion, is unpredictable as the sequelae of damage due to the acute phase of Chagas disease cannot be foreseen. Prevention and control There is no vaccine against Chagas disease and no immunotherapy. With the aim of activating a Th1 immune profile with stimulation of

 CD8+ T cells, several experimental vaccines, including recombinant proteins, DNA and viral vectors, and heterologous prime-boost com- binations have proved immunogenic and protective against mor- tality in mice. However, there have been no clinical trials. Chagas disease flourishes where there is poverty and poor housing conditions. There are proven methods of controlling domestic triatomine bugs. These depend on insecticide spraying, health edu- cation, community support, and house improvement. Synthetic pyrethroids are the insecticides of choice and several commercial sources are available. Vector control programmes consist of prepara- tory, attack, and vigilance phases. In the preparatory phase, the dis- tribution of all dwellings must be mapped, the presence of infested houses assessed, and the attack and vigilance phases costed and planned. The attack phase involves high quality spraying all houses and peridomestic buildings, irrespective of whether bugs have been found. During the vigilance phase, the community plays an essential role in reporting residual bug infestations, which elicit a

rapid re- spraying response for the affected and neighbouring houses. Serology is vital for monitoring the success of control programmes. Children born after control programmes begin should be serologically nega- tive beyond 9 months of age (to exclude transplacental transfer of IgG) except for infrequent cases of congenital transmission. Blood donors in or from endemic areas should be screened sero- logically. If emergency conditions demand the use of seropositive blood, it can be decontaminated with crystal violet (250 mg/litre) and storage at 4°C for at least 24 h. Organ donors or recipients who are potentially infected should be screened serologically. Seropositive immunosuppressed recipients are likely to suffer reactivated acute- phase infection. Prophylactic chemotherapy with benznidazole may be effective. The Southern Cone programme launched a massive effort to elim- inate T. infestans from Argentina, Bolivia, Brazil, Chile, Paraguay, Uruguay, and southern Peru. Domestic infestation in Brazil has been reduced by 85%. Uruguay and Chile are essentially free of vector- borne and blood transfusion transmission. Substantial progress has also been made in the other participating countries. However, triatomine infestation and high prevalence of T. cruzi infection re- main persistent and urgent public health problems in parts of the Gran Chaco region of South America, particularly among indi- genous communities. Similar international collaborations have been initiated in Central America and the Andean Pact countries. Reinvasion of sylvatic bugs into domestic habitats may compli- cate vector control in some regions. One example is T. brasilien sis in north-eastern Brazil, which reinvades houses from adjacent rock piles. A second example is R. prolixus, which, in some regions of Venezuela and Colombia, has the capacity to reinvade houses from adjacent infested palm trees, as demonstrated by compara- tive triatomine population genetics. A surveillance programme and rapid responses to new domestic triatomine populations has been planned to protect the Amazon against domiciliation of vectors. Unanswered questions and future research T. cruzi is of immense research interest. It is not yet entirely clear how the organism evades the host immune response; the patho- genesis of Chagas disease is not fully understood. Further research is required, especially to produce a nontoxic, low-cost oral drug, which would eliminate the reservoir of infection in humans. New drugs are under development via the Drugs for Neglected Diseases initiative (DNDi). Drug discovery will be aided by new mouse models with transgenic bioluminescent T. cruzi strains, which have suggested prolonged sequestration of chronic infection in the alimentary tract. An improved, standardized universal, point of care, rapid diagnostic test is required, and post-chemotherapeutic biomarkers of cure. Peptide-based T. cruzi lineage-specific ser- ology may contribute to understanding the unclear association be- tween sequestered T. cruzi genetic lineages, clinical presentations, and and the complexity of transmission cycles. Molecular methods have already radically changed our understanding of T. cruzi and they will continue to clarify the epidemiological significance of di- verse and hybrid strains, and genetic exchange in natural popu- lations. High resolution comparative genomics of T. cruzi may provide incisive new insight. The origins and evolution of the or- ganism and its vectors are also of considerable academic interest. Trypanosoma rangeli The second human trypanosomiasis in the New World is due to T. rangeli infection. T. rangeli is also transmitted by triatomine bugs, in particular the genus Rhodnius. In Rhodnius species, how- ever, T. rangeli traverses the wall of the alimentary tract, infects the haemocoel, and reaches the salivary glands, in which the metacyclic infective trypomastigotes are produced. T. rangeli is thus transmitted by the bite of the triatomine bug and not by contamination with bug faeces. Although enzootic T. rangeli infection is widespread in Latin America, transmission to humans is virtually confined to areas in which R. prolixus is the domestic vector of T. cruzi. Coinfections of T. cruzi and T. rangeli may occur. The organism appears to be nonpathogenic in humans. T. rangeli can be pathogenic to Rhodnius species. The importance of T. rangeli lies in the fact that it may con- fuse xenodiagnoses or blood culture to detect T. cruzi.

With care and experience, T. rangeli can be distinguished from T. cruzi either by its long slender epimastigotes (up to 80 µm in length) and its smaller kinetoplast or by its presence in the haemolymph or salivary glands of some xenodiagnosis bugs with established infections. The life cycle in the mammalian host is uncertain, but T. rangeli is thought Fig. 8.8.12.10 Trypanosoma rangeli in a blood smear from an infected mouse. Courtesy of J. Williams.

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