Tropical diseases encountered in Canada: 1. Chagas’ disease

H. Schipper, B A SC, MD, FRCP[C]; B.M. McClarty, MD; K.E. McRuer, MD; R.A. Nash, MD; C.J. Penney, B A SC, MD

Chagas’ disease, or South American trypanosomiasis, is an endemic South American disease now being seen in Canada in both acute and chronic forms. It is characterized by an initial parasitemia that elicits a brisk immune response. Evidence is mounting that the debilitating chronic form, which is characterized by cardiac and visceral organ failure, results from antigenic cross-reactivity between the parasite and the human host, which generates an aberrant, destructive, cell-mediated immune response. Diagnosis, treatment and potential areas for investigation are discussed.

La maladie de Chagas, ou trypanosomiasi sud-américaine, est une maladie endémique en Amérique du Sud que l'on rencontre maintenant au Canada dans ses formes aiguë aussi bien que chronique. Elle est caractérisée par une parasitémie initiale provoquant une vive réaction immunitaire. On note l'accumulation de plusieurs indices à l'effet que la forme chronique débilitante, qui est caractérisée par une défaisance du cœur et des organes viscéraux, résulte d'une réaction antigénique croisée entre le parasite et l'hôte humain. Ceci provoque une réaction immunitaire à médiation cellulaire, aberrante et destructrice. Le diagnostic, le traitement et les champs éventuels d'investigation sont discutés.

South American trypanosomiasis, which was first described by Chagas in 1909,1 is a disease endemic in South America (Fig. 1) that has been considered rare elsewhere. Unlike malaria and the hygiene-dependent dysenteries, whose victims are often short-term visitors in whom the disease incubates during their return home, Chagas' disease is more to be expected in persons who have recently emigrated from South America. Political and economic tensions have increased emigration from Chile, Colombia, Ecuador and Argentina, where the disease is endemic, and Canada has been a willing refuge. In 1976 there were 10 628 known immigrants to Canada from South America.2

During 1971-76 nine cases of acute Chagas’ disease were diagnosed in Canada and recorded by the National Reference Centre for Parasitology.3 The number of chronic cases is unknown. The influx of persons from endemic areas increases the likelihood that both acute and chronic forms of the disease, as heralded by the cases reported to date, will be encountered in Canada.

Two cases of Chagas’ disease were seen in our centre within a 2-month period in 1978. A 47-year-old Argentinean immigrant of Chilean birth was noted to have congestive heart failure and the diagnosis was made as congestive car-

diomyopathy. His history of painless cardiac failure with episodic difficulty in swallowing for 6 years and intermittent urinary retention led to the suspicion of chronic Chagas’ disease. Fluorescent antibody tests for Trypanosoma cruzi gave confirmatory results. The second case, one of subacute South American trypanosomiasis, occurred in a child and was diagnosed post mortem (L. Montalvo-Hicks, C. Trevenen, J.N. Briggs: personal communication, 1978). The parents and siblings were sero-positive and therefore at risk for the chronic form of the disease.

Chagas’ disease is found throughout South America, from Central America to Chile and Argentina.
Only occasional cases have been described in the southwestern United States and Mexico, though the range of animal reservoirs is much more extensive there.⁵ In 1960 the World Health Organization estimated that 35 million people were at risk of infection and over 7 million people were affected.⁶,⁷ Chagas' disease is considered to be primarily a disease of the lower social classes, as the night-biting insect vectors reside in the cracks and thatch of poorly constructed buildings. In endemic areas chagasic myocarditis is responsible for about 25% of all deaths in persons between the ages of 25 and 44 years and is the most common cause of cardiac disease.⁷ As a general rule visitors do not stay for long under these conditions. None the less, persons returning from more remote areas in endemic regions, particularly if their accommodation was rugged or they had extended visits with rural families, would seem to be at risk for both the acute and the chronic forms of the disease.

The parasite

The causative organism of Chagas' disease is *Trypanosoma cruzi*, a flagellate related to both *Trypanosoma brucei*, which causes African sleeping sickness, and *Leishmania* spp., which cause kala-azar and cutaneous leishmaniasis. The insect vector is a hematophagous reduviid bug, and the disease reservoirs include infected humans, domestic animals such as dogs and cats, and wild animals, especially rodents, opossum and armadillos.⁸⁻¹⁰

The flagellated trypanosomes are ingested by the insect while it is feeding upon infected animals. The organisms multiply in the gut of the bug and after 15 to 30 days develop into the infective metacyclic trypanomastigotes. These are excreted in the feces and enter a new host through contamination of a bite or another break in the skin surface. This contaminative transmission is distinct from the inoculative transmission of African trypanosomiasis, in which the infective trypanomastigotes are associated with the mouth parts of the insect vector and are transmitted to the new host by the bite. Chagas' disease is also transmitted through transfusion of contaminated blood, and the organisms can cross the placenta.¹¹,¹²

The infective trypanomastigotes do not multiply in the bloodstream of the host. Rather, they invade the reticuloendothelial system, striated muscle and cardiac muscle, where they are transformed into leishmanialike amastigotes. Multiplication of the amastigotes by binary fission results in a pseudocyst or "nest". The amastigotes are then transformed into epimastigotes and trypanomastigotes. The cells rupture, releasing these infective forms, which in turn may invade other cells or be ingested by a reduviid, completing the cycle (Fig. 2).⁴

Clinical presentation

Clinically the disease may be divided into three phases: acute, latent and chronic.¹³
Acute Chagas' disease

Following an incubation period of 1 to 3 weeks, during which the amastigotes proliferate and the trypomastigotes enter the bloodstream, the acute stage is seen. This is characterized by high levels of parasitemia resulting in toxic manifestations and reticuloendothelial activity. It is usually seen in children between the ages of 1 and 5 years. The infective metacyclic forms of the organism elicit an intense local reaction, with edema and some cellular infiltration (the chagoma). The unilateral or bilateral facial and palpebral edema seen in children (Román’s sign) suggests conjunctival penetration. One can easily imagine a sleepy child scratching reduviid feces on his or her contaminated legs and transferring the infection to the conjunctiva by rubbing the eyes. Dissemination to the local lymphatics leads to lymphadenopathy and generalized reticuloendothelial activity. As the life cycle of the trypanosome is repeated within the human host, more and more organ systems are involved. Despite this "classic" description, the presentation is so variable that in endemic areas Chagas' disease is included in the differential diagnosis of any persistent febrile illness with lymphadenopathy and edema in a child. Hepatosplenomegaly and lung involvement may be found when the parasites disseminate throughout the body. The parasites invade the autonomic ganglia and muscle of the esophagus, colon, heart and other hollow viscera. Rarely acute meningoencephalitis results, the sequelae of which include spastic paralysis, mental deficiency and cerebellar symptoms.16

The most serious clinical presentation is one of severe and intensifying myocardial damage, with tachycardia, arrhythmias, cardiomegaly and heart failure, which may be fatal with the first attack. The 10% mortality during the acute phase is attributable to heart failure or meningoencephalitis.18 Patients who survive the initial illness may experience remissions and recrudescences of the disease, with progressive acute deterioration in cardiac function, or the disease may become latent and chronic immune-mediated cardiomyopathy may develop.

The latent period

The latent period represents the interval between the end of the acute phase of the disease and the detection of clinical cardiac or visceral ganglioneuropathic abnormalities. Its duration, averaging about 12 years, depends on a number of factors, including the presence of other cardiac abnormalities, the cardiac reserve at the end of the acute phase, the intensity of the immunologic response and other cardiac stresses. During this time the patient is asymptomatic and the disease is usually only detectable by immunologic methods. Though it has proven difficult to accumulate accurate population statistics, it is generally held that chronic Chagas' disease develops in approximately 10% of all patients with serologic evidence of latent disease.16

Chronic Chagas' disease

The hallmarks of chronic Chagas' disease are progressive ganglioneuropathy and very low levels of parasitemia. The immunologic implications of this syndrome are the subject of aggressive investigation that is beginning to yield results. The most frequent and best described clinical manifestations are cardiac, though significant noncardiac involvement is not uncommon.

The principal symptoms of chronic chagasic cardiac disease are congestive cardiac failure (usually right-sided), arrhythmias and precordial pain not due to coronary artery ischemia.17 Stokes–Adams attacks may also occur. Pulmonary or systemic embolism from mural thrombi may be the first manifestation of the disease.18 Functionally the most important lesion is progressive diffuse myocarditis.19 However, there are few, if any, gross cardiac lesions that are considered pathognomonic. Köberle,20 among others, considered the chronic form of Chagas' disease to be a neuromyopathy, which would explain in part the prolonged latent period. This neuromyopathy leads to progressive autonomic dysfunction of the heart and other organs, and may account in some measure for the bizarre apical myocardial herniations observed. Likewise, conduction abnormalities and sudden death are manifestations of myoneural dysfunction of an organ in which very short-term alterations in electrical function can have catastrophic results. Thus, diagnostic testing will reveal a constellation of findings that suggest the disease, but none of which can establish the diagnosis.

Conduction defects are seen in two thirds of patients with this disease; right bundle branch block is the most common. Left anterior hemiblock, multifocal premature ventricular contractions and negative symmetric T-waves are also frequent but are not diagnostic.21,22 Vectorcardiography is useful for localizing lesions and following the progression of the disease.23 Echo-cardiography, while not diagnostic, is useful in establishing a diagnosis of congestive cardiomyopathy. Puigbo and associates24 have proposed a system for staging chronic Chagas' disease (Table I).

Marked denervation of the esophagus, colon, bronchi and other hollow viscera, with resulting visce-romegaly, is also seen.25 Related symptoms include dysphagia, constipation and urinary retention. Organomegaly is more common in southern South America than in Central America or northern South America.26 The reason for this disparity is unclear.

Pathological features

The gross morphologic findings at autopsy are consistent with diffuse ganglioneuropathy and its attendant functional sequelae. In the heart, enlargement and generalized hypertrophy and dilatation are found. On the epicardial surface prominent vascular congestion and focal epicardial thickening are common.27,28 Apical herniation is considered by some to be pathognomonic of the disease,29 and apical thrombosis with focal endomyocardial fibrosis at the base is highly suggestive.30 Generally vascular and valvular lesions are absent.

The myocardial dysfunction resulting from these lesions is
reflected in secondary findings, primarily passive congestion and thromboembolism in both the pulmonary and the systemic circulation, common sites being lung, kidney, spleen and brain.44

Similar findings characteristic of the visceroganglioneneuropathy seen in noncardiac Chagas' disease include megaesophagus, megacolon and megareter.

The microscopic abnormalities of chronic Chagas' disease suggest a cell-mediated immune response. Parasites are rarely seen. In acute cases nests of leishmania are almost invariably present, but in chronic cases one finds chronic diffuse myocarditis with focal areas of cellular infiltration. Myocardial biopsy reveals foci of mononuclear cell infiltrates, demonstrating a close relationship between lymphocytes and myocardial cells.19 With the use of transmission electron microscopy, imbrication of myocardial plasma membranes and disappearance of the basal lamellae have also been discovered. These lymphocyte aggregations are associated locally with microscopic evidence of muscle cell abnormality. There is frequently extensive fibrosis. Lending support to the contention that Chagas' disease is basically a ganglionopathy are the inflammatory changes seen in the cardiac conduction system,26 the intracardiac nerves and the autonomic nervous ganglia.77 Further, patients with chronic chagasic cardiac disease have been shown to have a significantly reduced number of ganglionic nervous cells in Auerbach's plexus of the esophagus even when there is no gross dilatation.84 In patients with overt organomegaly this disappearance of large numbers of nerve cells from Auerbach's plexus and focal inflammatory lesions akin to those seen in the cardiac form of the disease have been well described.24

**Immunologic considerations**

The long latent period, the rarity of overt parasitemia in the chronic stage of the disease, and the morpologic findings seen at biopsy and post mortem suggest that chronic Chagas' disease may well be the result of an immunologic process.

*T. cruzi* is a strongly immunogenic parasite. It has definite serologically typed antigenic structures. So far no correlation has been discovered between the different serologic types and the pathogenicity or geographic distribution of *T. cruzi*. There is also no evidence at this point of the antigenic variation seen in African trypanosomiasis and malaria that enables the causative organisms to evade the host's immune response.

Both humoral and cell-mediated immune responses have been demonstrated in patients with Chagas' disease.23 In response to the initial parasitemia the total serum gamma globulin concentration increases within 2 to 3 weeks and the number of parasites decreases. The presence of IgM is considered the earliest evidence of the acute stage of the disease.89 IgG levels rise shortly thereafter and persist for longer. It has been reported that with early chemotherapy both specific IgM and IgG may become undetectable.

After the initial antiparasitic response, which is largely humoral, cell-mediated immunity seems to be the most important factor in resistance to reinfecion and the development of chronic Chagas' disease.23 In experiments protection has been conferred by the transfer of lymphocytes from sensitized hosts to healthy animals.23 It has also been shown that activating or inhibiting the cell-mediated immune response results in a corresponding alteration in the parasitemia.

The host's immune system has been implicated in the development of chronic chagasic cardiac disease. It has been shown that a large percentage of patients with chagasic heart disease have a serum gamma globulin factor (the EVI antibody) reacting against the myocardium.19,23 The cellular structures reacting with the EVI antibody, as found by ultrastructural immunochimical methods, are the plasma membranes of the cardiac and skeletal muscle cells and of the endothelial cells of blood vessels.23 This suggests that there is cross-antigenicity between these tissues and *T. cruzi* since the antibodies are directed specifically against certain antigenic structures of *T. cruzi*.

Santos-Buch and Teixeira13 showed that sensitized lymphocytes were able to lyse rabbit heart cells from animals with or without parasitic infection. These sensitized lymphocytes had no lytic effect on corresponding renal cell cultures. The fact that lymphocytes that have not been sensitized to the trypanosome do not lyse rabbit heart cells, whereas lymphocytes from an identical strain of animal that have been sensitized to the parasite do

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**Table 1—System of Puigbó and associates15 for staging chronic Chagas' disease**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Stage 1</th>
<th>Stage 2</th>
<th>Stage 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms</td>
<td>Minimal</td>
<td>Minimal</td>
<td>Shortness of breath, peripheral edema, dizziness Congestive heart failure</td>
</tr>
<tr>
<td>Cardiac status</td>
<td>Normal</td>
<td>Moderate cardiomegaly Increasing segmental hypokinesis</td>
<td>Arhythmias, q waves in leads V1 to V6 Increasing mural thrombosis Decreased cardiac output, pulmonary hypertension</td>
</tr>
<tr>
<td>Fluoroscopic findings</td>
<td>Right bundle branch block, multifocal extrasystoles</td>
<td>Left anterior hemiblock, q waves in leads V1 to V6</td>
<td></td>
</tr>
<tr>
<td>Electrocardiographic findings</td>
<td>Apical thinning</td>
<td>Hypokinetic areas in left ventricle</td>
<td>Sudden</td>
</tr>
<tr>
<td>Gross cardiac abnormalities</td>
<td>Normal</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Cardiac hemodynamics</td>
<td>Hypertrphy and slight dilatation of left ventricle</td>
<td>Hypertrophy and dilatation of all chambers</td>
<td>Heart failure or thromboembolism</td>
</tr>
<tr>
<td>Ventriculographic findings</td>
<td>Arrhythmias</td>
<td>Sudden</td>
<td>—</td>
</tr>
<tr>
<td>Cause of death</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Histologic cardiac findings</td>
<td>Mononuclear cell infiltration, fibrosis of inner layers</td>
<td>—</td>
<td>Extensive fibrosis</td>
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lyse heart cells of animals without parasitic infection, must be considered strong immunologic evidence in favour of cross-reactivity between heart cells and the parasite. The sensitized lymphocytes react with normal myocardial cells by virtue of an antigenic site that is similar enough to a site on the trypanosome that the organism and the affected myocardial tissue are indistinguishable to the immunologically activated lymphocyte. The fact that such cross-reactivity is not seen with renal cells suggests that this common antigenic site is not found on renal cells. The clinical absence of chagasic nephritis seems to support this contention.

Thus, we favour the view that the chronic disease is primarily due to a persistent cell-mediated immune response, with some contribution from humoral immunity, in which cross-reactivity with host tissue results in cell lysis and cumulative damage over many years. The parasite causes an initial acute myocarditis that results in permanent cardiac damage. As well, it induces a cell-mediated immune response in which there is cross-reaction with normal myocardial cell membranes. The resulting immunologic assault leads to myocardial cell lysis and secondary fibrosis that is progressive and cumulative.

**Diagnosis**

Since Chagas' disease is endemic only in South America, the first step in the diagnosis (Fig. 3) is to find out where the person has travelled and, if that is suggestive, to determine whether he or she has lived under conditions in which the disease is transmitted. A history of insect bites with sequelae or even an acute episode of pertinent symptoms and signs may also be elicited. The development of an acute, progressive cardiomyopathy in a child, particularly if associated with fever and reticuloendothelial activity and an appropriate history, merits investigation for acute Chagas' disease.

The laboratory diagnosis of acute Chagas' disease differs from that of chronic Chagas' disease. In acute cases both a drop of blood under a coverslip and Giemsa-stained fixed blood smears should be examined for the typical C-shaped organisms. To facilitate the diagnosis in a mild infection one should lyse the blood cells and centrifuge the blood before examining the specimen for the organisms. Blood can also be centrifuged in a microhematocrit tube and the interphase examined for parasites. If the organism is not demonstrable in this manner other tests are available, xenodiagnosis being the most sensitive. This involves the examination of the rectal contents of laboratory-raised reduviid bugs 30 to 60 days after they have fed on the host. The test is tedious, slow and not without risk to laboratory personnel, but is the only test that will detect very low levels of parasitemia. Results are positive in 30% of chronic cases. Cultures of the patient's blood on a diphasic blood agar medium or intraperitoneal injection of 1 ml of the patient's blood into two albino mice and subsequent examination of the mice's blood every week for 1 month may also yield the diagnosis in patients with acute Chagas' disease whose parasitemia is mild. These tests are considered less reliable, however. During acute infection T. cruzi can frequently be cultured from the cerebrospinal fluid. This may be the case even in the absence of overt neurologic manifestations.

The presentation of relatively painless congestive heart failure without primary valvular disease in a patient with an appropriate but relatively remote geographic history suggests chronic Chagas' disease. Coexisting organomegaly or thromboembolic episodes, or both, should heighten one's clinical suspicion. Noninvasive cardiac diagnostic tests may be suggestive but are not diagnostic. Since the level of parasitemia is characteristically very low, immunologic diagnostic techniques are the most important laboratory aids.

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**FIG. 3—Steps in diagnosis of Chagas' disease.**
A complement fixation test will detect the presence of *T. cruzi* in 50% of acute cases and over 90% of chronic cases.29 False-positive results may occur in cases of *T. rangeli* or *Leishmania* infection. Many other serologic tests exist, but the most experience has been obtained with the indirect fluorescent antibody test and the indirect hemagglutination test. The former has been used in Brazil for serologic screening; fluorescein-labelled anti-IgM can be used to differentiate acute and chronic cases. The two tests yield positive results earlier in the infection than the complement fixation test, which, however, is said to be more specific.

It has generally been found that serologic positivity persists for life in untreated patients.30 In some endemic areas 50% of the population show serologic positivity, but most are symptomless. It has been stated that over 24 years approximately 10% of all serologically positive individuals will manifest clinical Chagas' disease.31

### Treatment

The most effective therapeutic agent for acute Chagas' disease is a 5-nitrofururan, Lampit.3728 It eliminates the circulating parasites, but there is some doubt as to its ability to eliminate the intracellular parasites at doses tolerable to the patient. The drug is administered for 120 days. Side effects become obvious in the last 40 days. The claimed success rate is 90% under optimal conditions. It has also been claimed that Lampit is effective in reducing the parasitemia in the chronic stage of the disease.39

Recent investigations with Lampit have shown that administration of the drug is associated with a return to normal of the results of a number of tests, including skin tests and leukocyte migration inhibition, that demonstrate depressed cell-mediated immunity in chronic Chagas' disease. It is thought that the drug may alter the immune response rather than act on the parasite. The implications of this are unclear and are under investigation.3940

Another promising chemotherapeutic agent is a 2-nitroimidazole that is proving to have an effect on the intracellular parasites in the acute stage of the disease.

Recently the antihypertensive agent allopurinol has been demonstrated to have a marked in vitro effect on the trypanosomes. It appears that *T. cruzi* metabolizes allopurinol sequentially to allopurinol mononucleotide and allopurinol mononucleotide; the latter exerts its antitypanosomal action through its incorporation into the ribonucleic acid of *T. cruzi*.41 The relative specificity of this metabolite of a generally innocuous agent offers considerable promise for clinical application.

Work is also progressing with derivatives of 8-aminoquinolones. This family of drugs may become more important in the future because concern is now arising over the mutagenic and carcinogenic properties of the nitrofurans and the nitroimidazoles. Neurotoxic effects have also been demonstrated in long-term users of nitroimidazoles.42 Should these concerns be substantiated the 8-aminoquinolones and allopurinol analogues may emerge as the preferred chemotherapeutic agents for Chagas' disease.

The overt forms of chronic Chagas' disease are not amenable to antitypanosomal therapy. At present, therefore, treatment must be symptomatic. The chronic cardiomyopathy is treated with digitalis and diuretics. Surgical intervention may be necessary for problems associated with organomegaly. There is no evidence that direct pharmacologic stimulation of the affected ganglia is of benefit. Possibly, as the immunologic derangement now being associated with Chagas' disease becomes better elucidated, pharmacologic manipulation of the immune system may emerge as an important therapeutic measure.

The immunogenicity of the trypanosome suggests a possible role for vaccination.283743 This holds promise for three reasons. The antigenic variation known to exist among the agents causing African trypanosomiasis and malaria has not been shown in *T. cruzi*. Cross-protection between strains of *T. cruzi* has been demonstrated, and strains that are nonreproducing or nonvirulent have been produced. Vaccines containing live organisms of low virulence induce good resistance to reinfection with virulent strains, but these vaccines can theoretically produce chronic Chagas' disease. The vaccines containing nonreproducing strains, which are produced by disruption under pressure, and mixtures of amastigotes and trypomastigotes that have been irradiated appear to be the most effective.44 It is only recently that significant protection with vaccines containing nonreproducing strains has been attained. The effects on the chronic disease of vaccination with both types of preparation have yet to be assessed.

### Conclusion

Chagas' disease is an acute parasitic disease of children that induces a brisk humoral and cell-mediated immune response. In most cases this leads to substantial clearance of the parasite. In a proportion of patients, however, chronic, indolent cytotoxic immunologic hyperactivity persists, resulting in myocardial destruction and visceral ganglioneuropathy. There is mounting evidence for trypanosomal–myocardial cross-antigenicity.

The principal thrusts of research are toward vaccination and systemic chemotherapy. The elucidation of the immunologic features of the disease and the observation that effective drug therapy alters the patient's immunity suggest that control of the aberrant immune response may prevent the development and progression of cardiac and visceral organ failure.

This is not a disease in which the risk is one of further transmission within a temperate zone community. Rather, it is a disease in which missed diagnosis in the rare case of acute disease may be fatal despite improved drug treatment. The diagnosis of chronic Chagas' disease in a patient with congestive heart failure or organomegaly, or both, and an appropriate social and geographic history, may prevent needless costly and hazardous extended investigation. Follow-
up of family members may reveal further early chronic cases and even the occasional unsuspected acute infection.

The study of this ancient disease demonstrates how the application of recently introduced immunologic and biochemical techniques can further our understanding of human host–parasite relations. In time, one hopes, treatment specific for the different pathogenetic processes of acute and chronic Chagas' disease will result in a substantial improvement in our ability to alleviate this, the commonest cause of early death from cardiac disease in South America.

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