Chapter 1

AMERICAN TRYPANOSOMIASIS (Chagas' Disease)

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Definition. — American trypanosomiasis (Chagas' disease) is a zoonotic disease caused by the protozoan *Trypanosoma cruzi* (Chagas 1909). This organism causes acute or chronic parasitemia and parasitization of parenchymal cells of many organs, especially heart, brain, esophagus, and colon. Another American trypanosome, *Trypanosoma rangeli* (Tejera 1920), produces a mild parasitemia in man which may persist for months or years, but does not invade or destroy tissue cells nor cause other evidence of disease.

Epidemiology. — Bugs and mammals infected with *T. cruzi* have been found on the American continents between latitudes of 42N (northern California and Maryland) and 43S (southern Argentina and Chile), and on the islands of Aruba and Trinidad. Infection of man is unknown on other Caribbean Islands and is exceedingly rare in the United States and Mexico, but is present in all Central and South American countries (Fig. 7-1-1).

Fig. 7-1-1. Distribution of Chagas' disease in man and distribution of some significant vectors of *T. cruzi*. AFIP 65-5015.

Because of difficulties in detecting low-grade parasitemias, the expense of extensive serological surveys, and the insidious nature of chronic Chagas' disease, prevalence can only be estimated. Infection by *T. cruzi* is most often acquired by rural and suburban poor people whose homes (Fig. 7-1-2) and

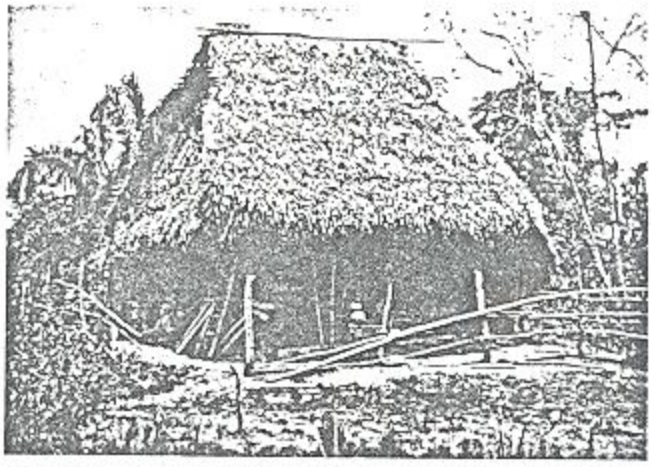


Fig. 7-1-2. Home of patient with acute Chagas' disease. *Rattus rattus* and *Rhodhius pallescens* infected with *T. cruzi* were present. Note the roof of corozal palm and walls of mud and lath. AFIP 75-4181. (Photograph contributed by Gorgas Memorial Laboratory.)

ways of life permit close contact with infected bugs. Some species of triatomid are sylvatic and rarely infect man; others such as *Triatoma infestans, T. sordida,* and *T. dimidiata* are domestic or paradomestic and cause thousands or millions of infections in man. Probably 5 to 10 million South Americans and several hundred thousand Central Americans are infected by *T. cruzi.*

Infections of bugs, man, and other reservoir hosts with *T. rangeli* have been found with variable prevalence in most Central and South American countries. This variation depends on distribution and on sampling. *T. rangeli,* uncommon in Peru, Chile, Argentina, and Brazil, is most common in Venezuela, Colombia, and Panama.

Transmission. — Forty species of 9 genera of triatomid (reduviid) bugs (Fig. 7-1-3) transmit *T. cruzi*. *T. cruzi* can also develop in some bedbugs and ticks. A bug may remain infected for life (several years). Larvae, nymphs, and adult bugs ingest trypomastigotes (trypanosomes) when taking blood meals from infected animals. The parasites then multiply and differentiate in the alimentary tract of the bug from transient amastigotes (leishmanial forms), to epimastigotes (crithidial forms), and finally to metacyclic trypomastigotes. The latter congregate in the rectum of the bug and are discharged in its feces. Infection of mammals takes place by ingestion of infected bugs and also by contamination of mucous membranes, conjunctivae, and abraded skin with fecal material from infected bugs. Reservoir hosts of *T. cruzi* include marsupials, edentates, bats, rodents, carnivores, pigs, and primates.

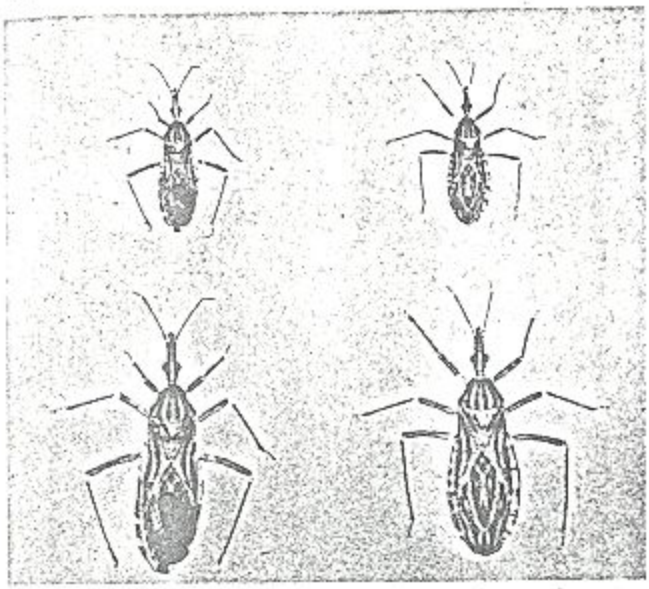


Fig. 7-1-3. Adult reduviid bugs, *Rhodnius prolixus,* a common vector of *T. cruzi*. Male is upper left, female is upper right—actual size. Male is lower left, and female is lower right. X1.6, AFIP 70-7300, 73-6612, 73-6613. (Bugs raised and contributed by Mr. Ronald C. Neafie, AFIP.)

T. cruzi infections of man have been acquired by blood transfusion, by accidental contamination with infected blood or cultures in laboratories, and congenitally by transplacental passage of parasites.

Less is known about the transmission of *T. rangeli,* but *T. rangeli* is transmitted by only a few species of triatomid bugs, most or all of which belong to the genus *Rhodnius*. Infection by blood meal and multiplication and growth of various forms in the alimentary tract of the bugs proceed as with *T. cruzi,* except for the site of the development of metatrypanosomes. About 6 weeks post-infection, flagellated parasites penetrate the gut wall, pass through the hemocoelom and invade the salivary glands of the bug. Here, metacyclic trypanosomes develop and multiply. Thus, the actual bites of infected bugs transmit *T. rangeli,* a more efficient mechanism than the fecal contamination method of *T. cruzi.*

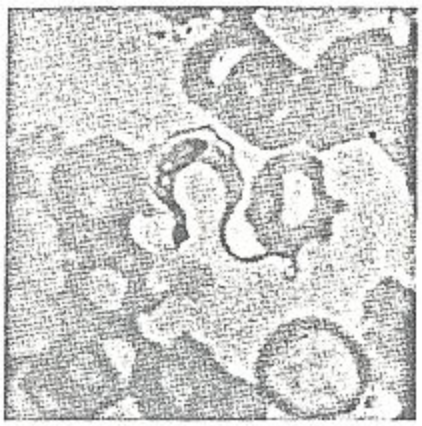
Etiologic Agent and Laboratory Diagnosis. — In man trypomastigotes circulate in the blood (Color 7-1-A1,2,3) and amastigotes live in cells (Color 7-1-A4 to 7). Trypomastigotes of *T. cruzi* can be distinguished from other species by a tendency to assume a "C" or "U" shape when fixed, by the location and size of the kinetoplast at the extreme posterior (aflagellate) end, by its narrow undulating membrane, and by its length, 16-22 microns (Color 7-6-A1,2). The trypomastigote of *T. rangeli* has a broader undulating membrane, a less prominent kinetoplast located between the compact nucleus and the posterior end, and is longer, 27-32 microns (Color 7-1-A3).

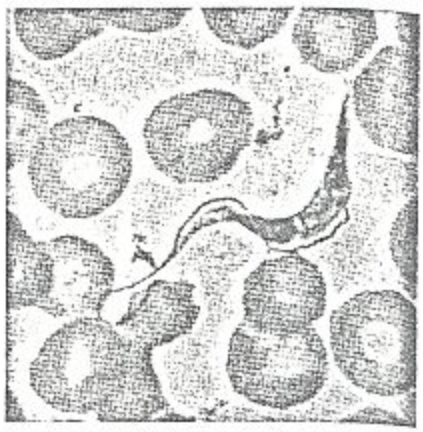
Trypomastigotes of *T. cruzi* can probably invade many types of mammalian cells. In doing so, they lose their flagella and undulating membranes, and become amastigotes (leishmanial forms) capable of repeated divisions by fission. Amastigotes are present in greatest numbers in myofibers (Color 7-1-A4), in considerably fewer numbers in the brain (with the exception of congenital infections), and, occasionally, in small numbers in other tissues. Cells of the reticuloendothelial system kill and digest amastigotes. The amastigote, 3 to 5 microns in size, can be recognized by the kinetoplast, a prominent bar, located within the cytoplasm and deeply stained by hematoxylin.

In tissue sections, the kinetoplast distinguishes *T. cruzi* from *Toxoplasma, Histoplasma,* and other microorganisms lacking a kinetoplast. Differentiation from *Leishmania* may be difficult but the kinetoplast of *T. cruzi* is larger than the kinetoplast of *Leishmania* Furthermore, leishmanias concentrate in phagocytic cells of the skin, mouth, nose, and throat, or in the macrophages of the reticuloendothelial system—all uncommon sites for *T. cruzi.* (For comparative illustrations of the small organisms see Color 7-6-A,B,C, in Chapter on Toxoplasmosis).

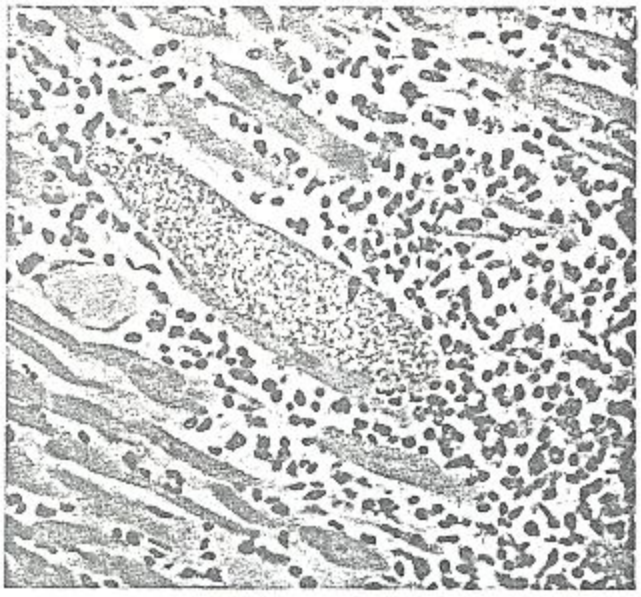
Parasitemia, usually present the third week after infection, is detected by microscopic examination of a fresh drop of blood, a stained thick smear, or the plasma in a hematocrit tube. The parasitemia is low-grade (1 to 5 parasites per thick smear) and persists for several weeks or months. Parasitemia, detected by xenodiagnosis or culture, however, may appear during the second week of infection and persist for weeks, months, or years.

Xenodiagnosis is done by allowing laboratory-reared triatomid bugs to bite the patient. If the patient has Chagas' disease, epimastigotes of *T. cruzi*

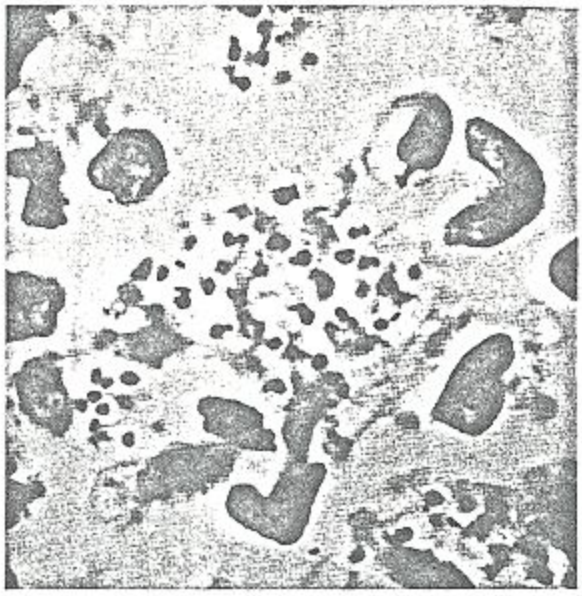




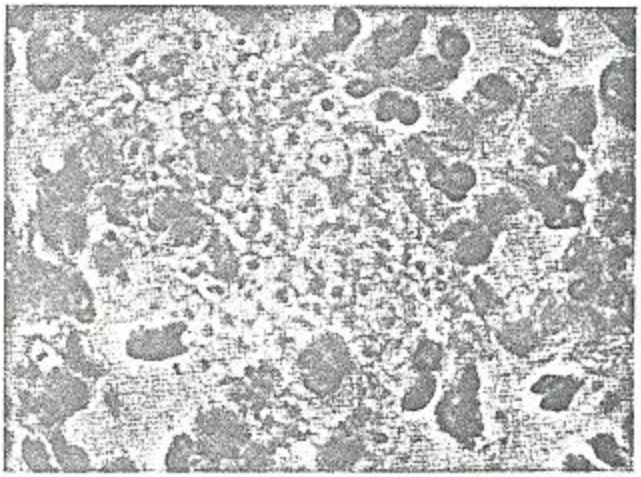
1. Thick blood smear with trypomastigote of *T. cruzi*. Note the C-shape of the organism and the terminal (posterior) location of the large kinetoplast. Giemsa, X1,700, AFIP 75-4182. (Photograph contributed by the Gorgas Memorial Laboratory, Panama.) 2. Thin blood smear with a trypomastigote of *T. cruzi* showing flagellum, nucleus, and terminal kinetoplast. Giemsa, X2,000, AFIP 73-1150. 3. Thin blood smear with trypomastigote of *T. rangeli* showing flagellum nucleus, and smaller kinetoplast a short distance from the posterior end. Giemsa, X1,800, AFIP 74-5195.



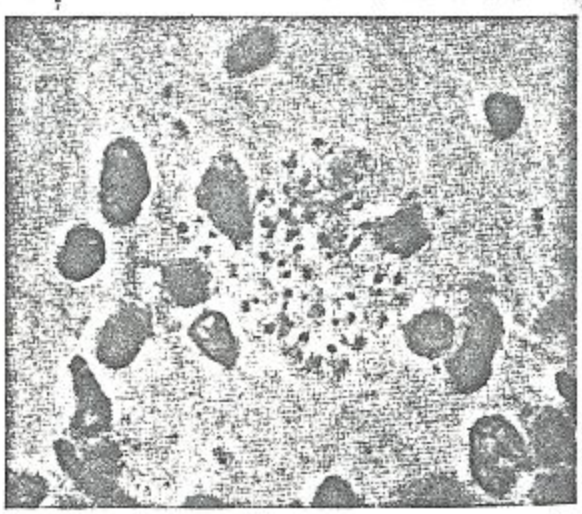
4. Heart. Acute Chagasic myocarditis with a myofiber filled with amastigotes. X400. AFIP 75-4185. (Photograph contributed by the Gorgas Memorial Laboratory.)



5. *T. cruzi* amastigotes in human testis. Observe the nuclei, cytoplasm and rod-shaped kinetoplasts. Reticulum stain, X1,800. AFIP 74-13233.



6. Acute Chagasic myocarditis with microabscess containing neutrophils and extracellular and phagocytosed *T. cruzi* amastigotes. X1,000. AFIP 75-4186. (Photograph contributed by the Gorgas Memorial Laboratory.)



7. Acute Chagasic encephalitis with amastigotes in glial cells of basal ganglia. X1,000. AFIP 75-4188. (Photograph contributed by the Gorgas Memorial Laboratory.)

appear in the bug's feces after 10 days.

Hemagglutinins and antibodies detectable by indirect immunofluorescence may be in serum 2 to 3 weeks after infection. Complement fixing antibodies are usually present 6 to 8 weeks post-infection. The overwhelming majority of people with acute *T. cruzi* parasitemia have no complaints and are unaware of their infection; that they had had parasitemia is usually an assumption based on positive serologic tests or the subsequent signs of chronic Chagas' disease.

Clinical Features. — Acute Chagas' disease. Although there is usually no history of a precise time of infection, this can sometimes be determined from dates of visits to endemic areas, transfusions, or, rarely, from the patient's memory of the presence of bugs, bites, or gross contamination. The bites of bugs, infected or not, produce transient urticaria in some people. A subcutaneous inflammatory nodule (chagoma) or nonpurulent unilateral palpebral edema and conjunctivitis with ipsilateral regional lymphadenopathy (Romana's sign) (Fig. 7-1-4) may appear 1 to 2 weeks after infection. When present,

Fig. 7-1-4. Child with Romana's sign. Unilateral conjunctivitis, palpebral and periorbital edema, and preauricular lymphadenopathy. AFIP 62-3934-6.

these signs mark the portal of entry. Many, however, become infected without these signs. Parasitemia, fever, localized or generalized edema, and moderate localized or generalized lymphadenopathy develop 2 to 3 weeks after infection and these signs are associated with myocarditis (arrhythmias, hypotension, tachycardia, distant heart tones, cardiomegaly (Fig. 7-1-5), hepatosplenomegaly), and encephalitis (irritability, drowsiness). Between 10 and 20 percent of patients die of myocarditis (irreversible cardiac failure or ventricular fibrillation). Survivors

Fig. 7-1-5. Roentgenogram. An enlarged heart 13 days after onset of *T. cruzi* parasitemia in a 46 year old man who died of acute myocarditis 3 days later. AFIP 74-5864. (Contributed by the Gorgas Memorial Laboratory.)

recover slowly and are often well 6 to 8 weeks after the onset. Some have persistent electrocardiographic changes, particularly right bundle branch block.

The early diagnosis of acute Chagas' disease depends on the demonstration of *T. cruzi* in thick smears. Serologic tests for hemagglutinins and immunofluorescent and complement fixation tests do not become positive for some weeks after infection. For instance, patients may die of Chagasic myocarditis and still have no detectable complement fixing antibodies. Cultures of blood and xenodiagnosis done on patients with acute Chagas' disease are uniformly positive, but the results are not available for 3 to 6 weeks.

Almost all patients with diagnosed acute Chagas' disease are treated with antitrypanosomal drugs (nitrofurans, 8-aminoquinolines, or metronidazole, Flagyl). These abolish the parasitemia but are less effective against the tissue amastigotes. Some patients "cured" of acute disease probably develop chronic Chagas' disease from recurrence or from reinfection.

Laboratory workers have been infected accidentally by animal blood or cultures and some of them have developed severe myocarditis. As yet, however, there are no reports of a fatal infection acquired in a laboratory. By contrast, infections acquired by blood transfusions are frequently fatal, probably because of the massive infective dose.

Congenital Chagas' disease. — In some pregnant women with parasitemia, the placenta and fetus are infected even without maternal symptoms. This commonly leads to abortion. In some parts of Chile and Brazil, congenital Chagas' disease may cause 10% of all spontaneous abortions. Most babies born alive with *T. cruzi* infections die within a few days or weeks of Chagasic encephalitis. Congenital Chagas' disease is uncommon and has not been reported in Central America, Colombia, and Venezuela. Congenital Chagas' disease should be distinguished from the common occurrence of a mother with a positive complement fixation (CF) test giving birth to a CF positive baby because of a transient persistence of maternal antibody in the baby's blood.

Chronic Chagas' disease. — Chronic Chagas' disease afflicts several millions of South Americans and thousands or tens of thousands of Central Americans. In most of these, chronic Chagas' disease develops years or decades after an episode of undetected parasitemia or, less commonly, following a recognized episode of acute Chagas' disease.

Chronic Chagas' disease is by far the most frequent and serious consequence of infection by *T. cruzi*. The principal manifestation is cardiopathy manifested by cardiomegaly and electrocardiographic evidence of right and left bundle branch blocks, A-V blocks, and multifocal ventricular extrasystoles, as well as the changes associated with necrosis of the cardiac apex. The clinical course varies from sudden death (probably caused by arrhythmias) to a slow but relentless loss of cardiac function and death during the last of repeated episodes of cardiac failure. Emboli from the ventricular apices or from the atria may give rise to cerebral and pulmonary infarcts, which complicate and shorten the clinical course.

In some parts of Brazil, Chile, and Argentina, patients with or without cardiopathy may have massive dilatation of various organs, more frequently of colon and esophagus and, less often, of bronchi, ureters, duodenum, and stomach. These so-called Chagasic "Mega" phenomena are strikingly absent in Venezuelan, Colombian, and Central American patients.

Diagnosis of chronic Chagas' disease depends on the clinical findings, a positive complement fixation test, and demonstration of the parasite, when present. Other serologic procedures, particularly, the immunofluorescent antibody test (IFA) may help. Parasitemia can be demonstrated by culture or xenodiagnosis in most patients with chronic Chagas' disease.

Pathology. — Acute Chagas' Disease. — The principal gross change is in the heart, which is enlarged and dilated. The myocardium is soft and pale, focally hemorrhagic and, in places, almost yellow (Color 7-1-B1). The body cavities contain excess serous fluid. Often there is pericarditis. The liver, lungs, spleen, and intestine are congested according to the degree of cardiac failure. The brain and meninges are congested and often contain petechiae. Microscopically, parasites are most numerous in the heart, are often present in the brain, and may be found in small numbers in any tissue or organ. In the heart, collections of amastigotes (and occasionally, trypomastigotes and epimastigotes) are present in the myofibers. Rupture of fibers is associated with microabscesses, phagocytosis and digestion of parasites, and an extensive and severe inflammatory reaction with lymphocytes, macrophages, and plasma cells (Color 7-1-B2). Fragmentation, vacuolization, hyalinization, destruction of myofibers, interstitial edema, and alteration of capillaries and veins are present. The coronary arteries are spared, but some degree of endocarditis and pericarditis is usual. Inflammation and parasitization of the sinus node and A-V node have been found, but these structures are usually less involved than the myocardium. Parasites invade neurons and glial cells of brain and spinal cord (Color 7-1-A7) and, less commonly, the perivascular spaces. Inflammatory reactions include perivascular cuffing by lymphocytes, focal infiltrates of lymphocytes in the meninges, and small nodules comprised of glial cells, lymphocytes, and plasma cells (Fig. 7-1-6). In addition, there may be infiltrates of lymphocytes and plasma cells in almost any organ or tissue.

COLOR 7-1-B CHAGAS' DISEASE

1. Anterior aspect, heart of 14-month old child who died of acute Chagasic myocarditis. Note dilatation of ventricles and pallor of the myocardium. AFIP 75-4183. (Photograph contributed by the Gorgas Memorial Laboratory, Panama.)

2. Acute Chagasic myocarditis. Note the extensive inflammatory cell infiltrates, interstitial edema, and separation of damaged myofibers. X250, AFIP 75-4184. (Photograph contributed by Gorgas Memorial Laboratory.)

3. Chronic Chagasic cardiopathy. Note aneurysm of left ventricle at apex and notched appearance of the apical aspect of the interventricular septum. AFIP 75-4189. (Photograph contributed by the Gorgas Memorial Laboratory.)

4. Chronic Chagasic cardiopathy. Note the indented thinned apical wall of the left ventricle and scarring of epicardium. AFIP 75-4190. (Photograph contributed by the Gorgas Memorial Laboratory.)

5. Chronic Chagasic cardiopathy with transilluminated apex viewed from above. The thinned scarred apex of the left ventricle transmits light, and there is extensive trabeculation of the left ventricular myocardium. AFIP 75-4191. (Photograph contributed by the Gorgas Memorial Laboratory.)

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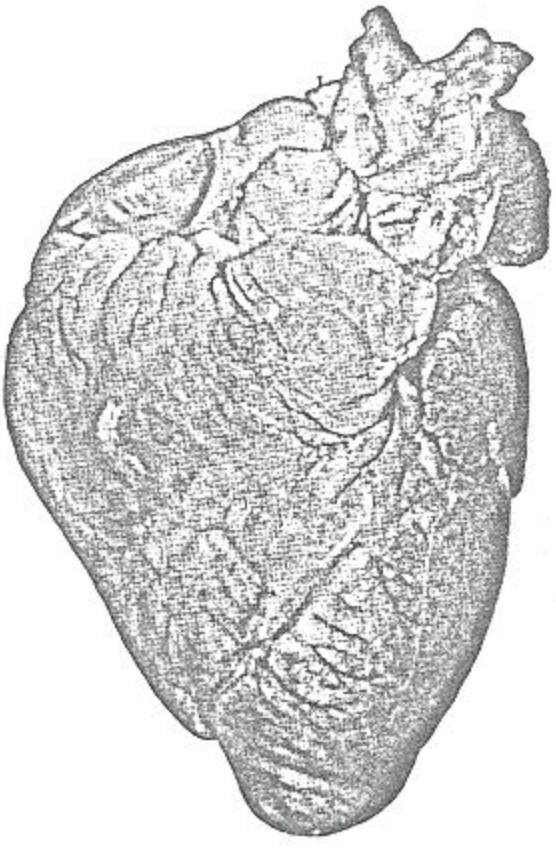

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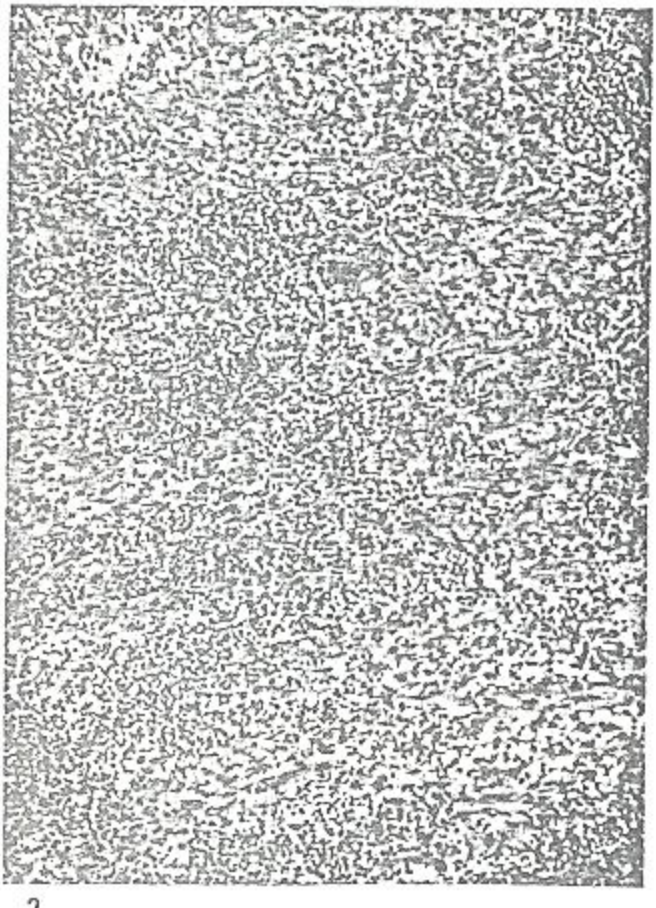

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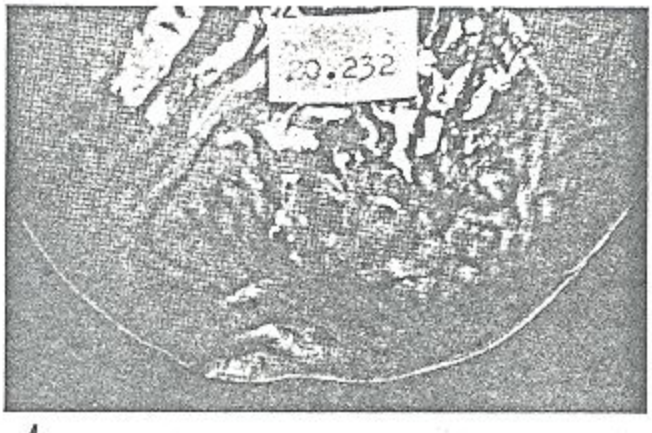

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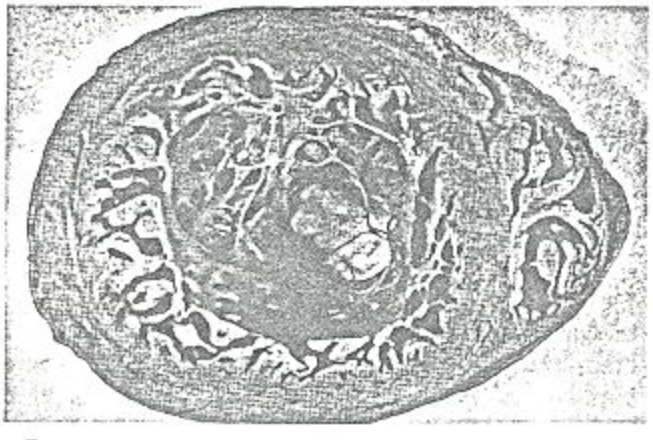

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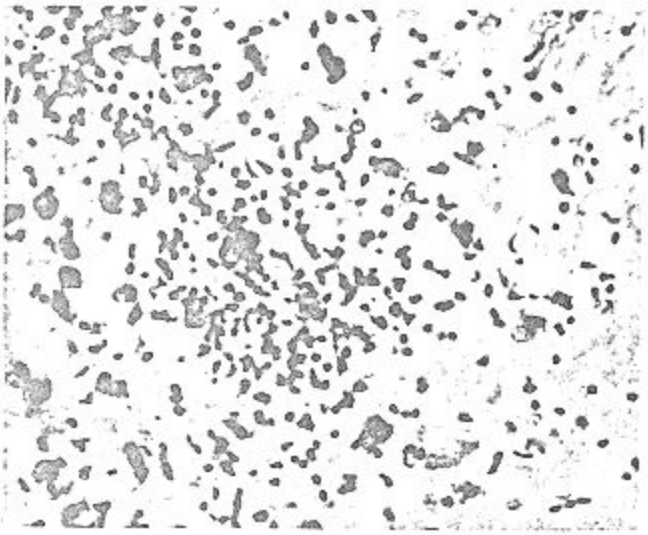

Fig. 7-1-6. Acute Chagasic encephalitis with an inflammatory focus of lymphocytes and glial cells in the basal ganglia. X250, AFIP 75-4187. (Photograph contributed by the Gorgas Memorial Laboratory.)

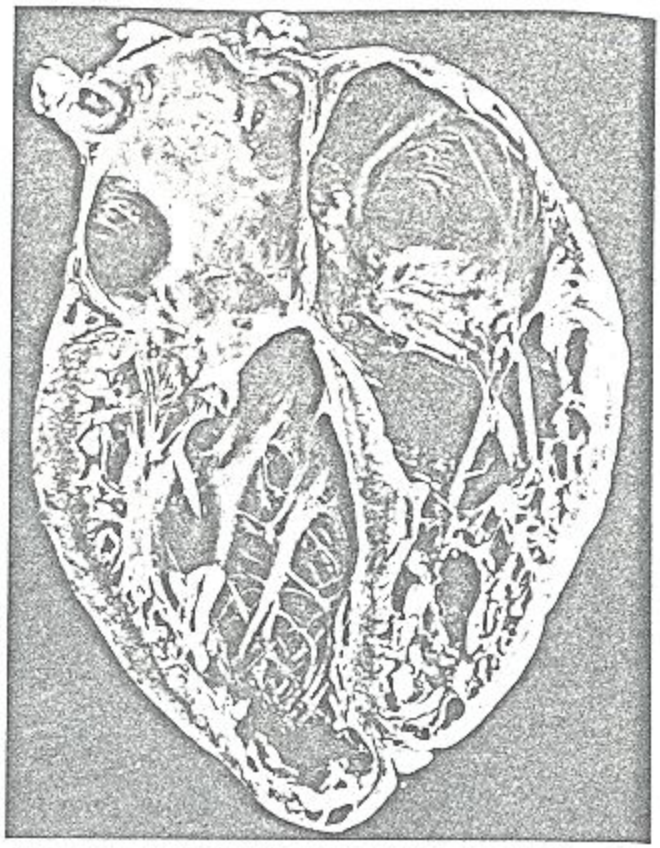

Fig. 7-1-7. Posterior half of a heart with chronic Chagasic cardiopathy. Note the dilatation and apical aneurysm of left ventricle, thinning of septum and ventricular walls, and the complexity of trabeculae near the insertions of the papillary muscles and the walls of the ventricles. AFIP 69-2961-2.

Congenital Chagas' Disease. — Congenital infections by *T. cruzi* usually cause abortion or stillbirth. In the relatively small number of live births in Brazil and Chile, there are reports of parasitization of the placenta and acute necrotizing encephalitis caused by numerous amastigotes and trypomastigotes. All lesions of acute Chagas' disease may be present in congenital Chagas' disease.

Chronic Chagas' Disease. — Chronic Chagasic cardiopathy is present wherever there is chronic Chagas' disease. In parts of Brazil and Chile, megaviscera, particularly megaesophagus and megacolon, are features of chronic Chagas' disease, but megaviscera have not been encountered in Central America, Venezuela, or Colombia—where chronic Chagasic cardiopathy exists. Chronic Chagasic cardiopathy represents the consequences of severe myocarditis. The heart is dilated, heavy (400 to 800 gm), and the right ventricular outflow tract is prominent. The valves are spared, but there is dilatation of the valve rings and dilatation and fibrosis of the atrial walls. The interventricular septum is deviated to the right, sometimes to the degree of immobilizing the adjacent tricuspid leaflet. The apices of the ventricles are thin, fibrotic, and almost devoid of myofibers. Rarely, the defect at the apex of the left ventricle forms an aneurysm (Color 7-1-B1); apical defects may be detected by palpation of the heart and by indentation with a finger or instrument (Color 7-1-B2). Distortion of the papillary muscles of the left ventricle and an increase in the number of trabeculae carneae in the distal parts of the ventricles are common (Fig. 7-1-7). Scars of the myocardium form streaks and bands anywhere in the ventricles, but are most frequent in the distal portions. Focal endocarditic and pericarditic changes are associated with chronic myocarditis and with severe dilatation. Although coronary arteries are usually normal, capillaries and small veins are dilated and irregular. Sometimes there are partially organized thrombi in the apical defects, among the trabeculae carneae, or in the auricular appendages. Microscopically, focal areas of chronic myocarditis contain infiltrates of lymphocytes and plasma cells and streaks and patches of interstitial fibrosis among hypertrophied myofibers (Fig. 7-1-8). Apical lesions regularly appear as segments of acellular fibrous tissue associated with epicardial vessels and adipose tissue (Fig. 7-1-9). In most series of chronic Chagasic cardiopathy, parasites are in fewer than 50% of the hearts, but prolonged search of multiple sections may demonstrate parasites more frequently. Fibrosis, inflammation, and atrophy with partial replacement by adipose tissue may be found in the A-V node or in the major conduction bundles. Koberle has found decreased numbers of ganglion cells in the posterior wall of the right atrium.

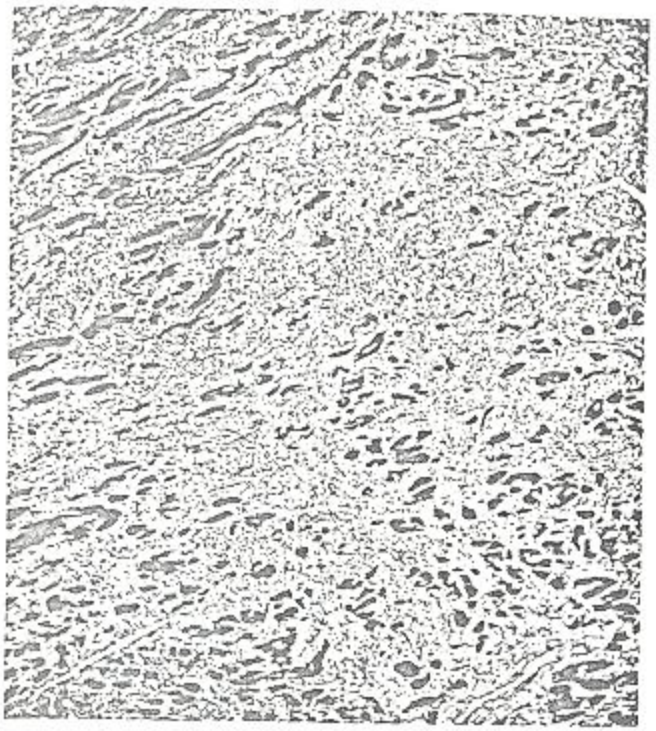

Fig. 7-1-8. Chronic Chagasic cardiopathy with scarring and chronic inflammation, left ventricle. X50, AFIP 63-4396.

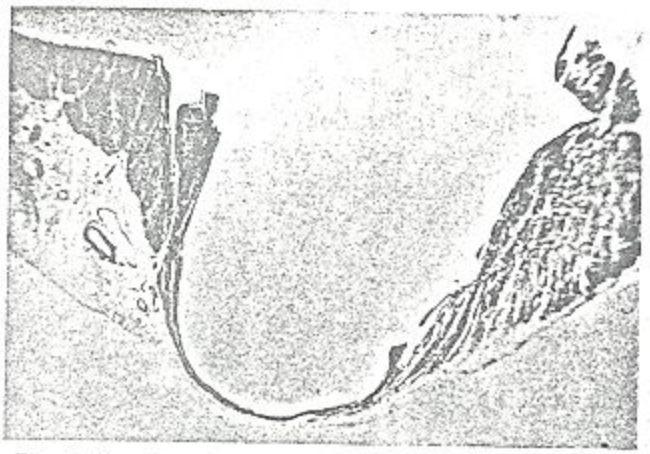

Fig. 7-1-9. Chronic Chagasic cardiopathy with thinned, amuscular, fibrous wall at apex of left ventricle. The coronary arteries in the adjacent epicardium are widely patent. Gomori trichrome, X5, AFIP 75-4192. (Photograph contributed by the Gorgas Memorial Laboratory.)

In megaviscera of chronic Chagas' disease, there is a profound decrease in the ganglion cells of the myenteric plexuses, and there is severe and characteristic distention and thinning of the visceral wall with variable amounts of scarring and chronic inflammation. The esophagus and colon are most frequently affected (Fig. 7-1-10).

Although encephalitis is present in acute Chagas' disease, there are no specific lesions of the central nervous system in chronic Chagas' disease. Some cerebral changes attributed to aging and vascular disease, however, may be sequelae of infection by *T. cruzi*.

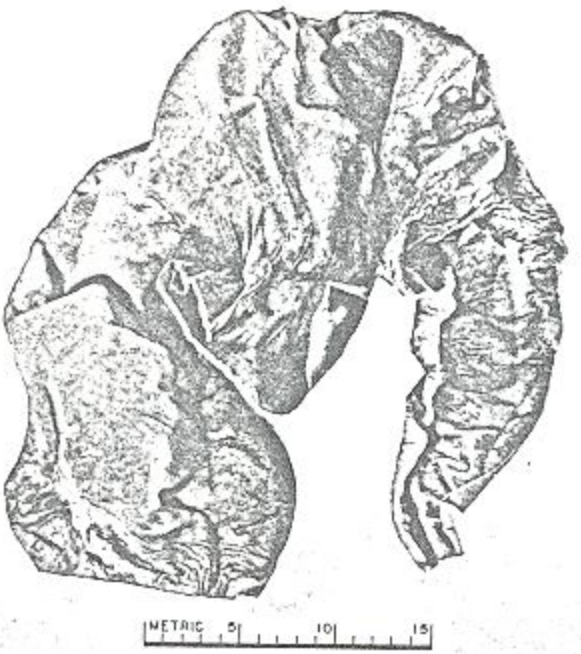

Fig. 7-1-10. Megacolon, chronic Chagas' disease. AFIP N-1872.

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