ANIMAL MODEL OF HUMAN DISEASE

Chagas' Disease in Inbred III/J Rabbits

ANTONIO R. L. TEIXEIRA, MD, PhD

From the Immunopathology Laboratory, Faculty of Health Sciences, University of Brasília, Brasília, Brazil

Biologic Features

Trypanosoma cruzi is a flagellate protozoan of the subgenus *Schizotrypanum*, whose life cycle in the vertebrate host includes blood trypomastigotes and intracellular amastigote forms. Macrophages and muscle cells are easily penetrated, but any cell type can be parasitized. Chagas' disease (American trypanosomiasis) is a complex of clinical manifestations that may result from infections with *T cruzi*. Its geographic distribution coincides with that of the parasite insect vector and is limited to tropical and subtropical regions of the American continent. Wild mammals that have become contaminated with feces of reduviid insects serve as *T cruzi* natural hosts and reservoirs. Humans and domesticated animals of European and African ancestors readily acquire the infections and may succumb to Chagas' disease.

Acute *T cruzi* infections usually occur in infancy and childhood, when large numbers of flagellates are present in the blood. The acute infections are clinically silent in over two-thirds of the individuals. However, in a minority of cases they can be manifested by indurated skin lesions at the port of entry of the parasite, fever, splenomegaly, and lymphadenopathy.[1] Manifestations of the acute infections subside spontaneously usually within 2–3 months. A phase of latency in which positive serologic tests are the only evidence of the infection may be interrupted in nearly half of the individuals by onset of electrocardiographic abnormalities.[2]

Chagas' heart disease is a common cause of disability and of mortality in endemic areas. Myocarditis seen in chronic Chagas' disease is characterized by mononuclear cell infiltrates and lysis of heart cells in the absence of the parasite *in situ*. Additionally, dilatation of the esophagus and colon, which is seen in a minority (<4%) of chronically infected individuals, is considered to be related to myositis and ganglioneuritis, leading to loss of parasympathetic neurons.

Animal Model

Changes similar to those described in humans naturally infected with *T cruzi* can be induced in inbred III/J rabbits (Jackson Laboratory, Bar Harbor, Maine) subcutaneously inoculated with cloned trypomastigotes of the Ernestina stock of the parasite derived from striated muscle cell cultures. Indurated skin lesions and increased satellite lymph nodes were found at the site of parasite inoculation in 10 inbred rabbits.[3] Parasitemia could be demonstrated in each *T cruzi*-infected rabbit, although they did not die in the acute phase of infection. In the absence of demonstrable parasitemia after the third month of infection, evidence of ongoing infection was shown by high titers of specific antibodies and by elicitation of delayed-type cutaneous reactions against a parasite microsomal antigen. Persistent electrocardiographic changes also were recorded in 90% of the rabbits, beginning 6 months after *T cruzi* inoculation. Increased cardiac silhouettes could be demonstrated in chest roentgenograms taken in the chronic phase of the infection (Figure 1).

Survival after *T cruzi* infection averaged 11.5 ± 5 months. The immediate cause of death could be at-

Publication sponsored by the Registry of Comparative Pathology of the Armed Forces Institute of Pathology and supported by Public Health Service Grant RR-00301 from the Division of Research Resources, National Institutes of Health, under the auspices of Universities Associated for Research and Education in Pathology, Inc.

Address reprint requests to Antonio R. L. Teixeira, MD, PhD, Immunopathology Laboratory, Faculty of Health Sciences, University of Brasilia, 70.910 Brasília-DF, Brazil.

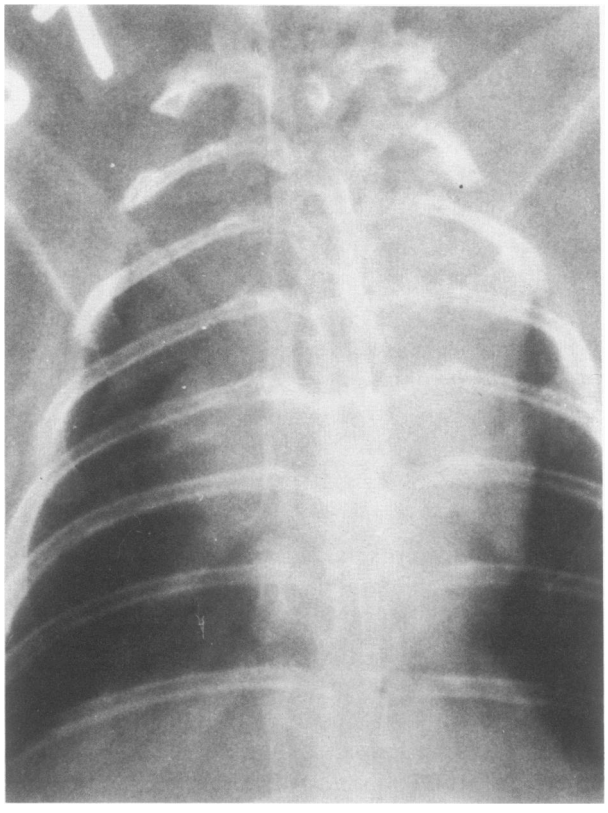

Figure 1—Increased cardiac silhouette in a rabbit 11 months after *T cruzi* inoculation.

tributed to chronic Chagas' disease in 60% of the rabbits with necropsy findings suggestive of congestive heart failure and/or pulmonary thromboemblism. Cardiomegaly with dilatation of the chambers was a conspicuous finding in these rabbits. Aneurysmal dilatation in the apex of the left ventricle (Figure 2) was another typical gross lesion of Chagas' disease in inbred III/J rabbits.

Histologically, the myocarditis of chronic Chagas' disease in the rabbit had features similar to those reported in humans. Lymphocytic infiltration and lysis of heart cells was always present, but the parasite could not be demonstrated in the lesions (Figure 3). The lack of evidence of direct parasite-induced necrosis of heart cells contrasted sharply with the abundance of uninfected myofibers destroyed in association with mononuclear cell infiltrates. Destructive inflammatory lesions also were seen in skeletal muscles and in the wall of the intestine. There also was ganglioneuritis and loss of myenteric, parasympathetic neurons. The focal nature of lesions observed in chronic Chagas' disease in rabbits is also a common feature of the human disease. Sequelae of these inflammatory lesions were multifocal fibrous scars commonly found in the heart.

Comparison With Human Disease

Chagas' disease in rabbits and that in humans have many similarities.[3-5] The acute phase of the infection in these hosts can go unrecognized, and patent parasitemia usually subsides spontaneously. In both, a phase of latency ensues in which the parasite is difficult to demonstrate, but immunologic test remain positive. A typical feature of Chagas' disease in humans and rabbits is the absence of correlation between parasitemia and morbidity and/or mortality. The onset of persistent electrocardiographic alterations in *T cruzi*-infected III/J rabbits were recorded after the sixth month of infection, when a strong delayed-type cutaneous reactivity to a parasite product could be elicited. Alterations of ventricular repolarization, ischemic changes, low amplitude of QRS complex, and arrhythmias (such as wandering pacemaker), conduction disturbances, and premature contractions were findings in rabbits similar to electrocardiographic changes that have been recorded in naturally infected humans.

Gross findings in rabbits with experimental Chagas' disease consist of cardiomegaly with dilatation of the chambers and aneurysmal formation at the apex of the left ventricle. The latter is characteristic of Chagas' disease in humans, and in endemic areas in Latin America it is useful in establishing the diagnosis. Effacement of the myocardium and fibrous sequelae are also common findings. The destructive microscopic lesions in the

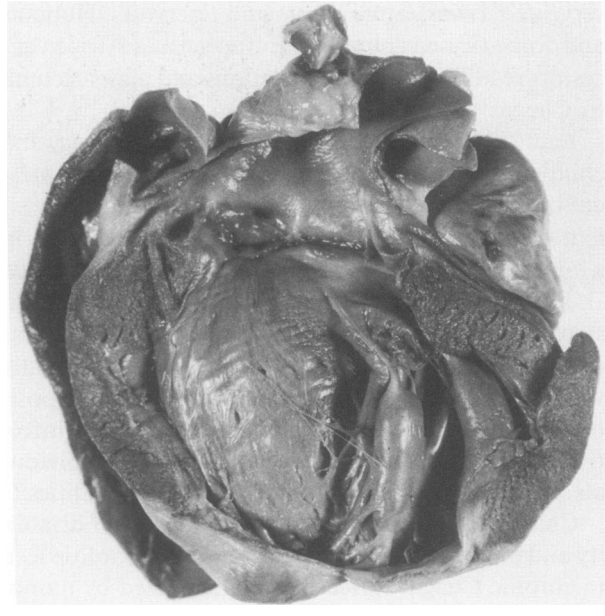

Figure 2—Cardiomegaly in an inbred III/J rabbit 16 months after *T cruzi* inoculation. Notice dilation of cardiac chamber and aneurysmal formation in the apex of the left ventricle. A fibrous scar replaces the myocardium at the apex.

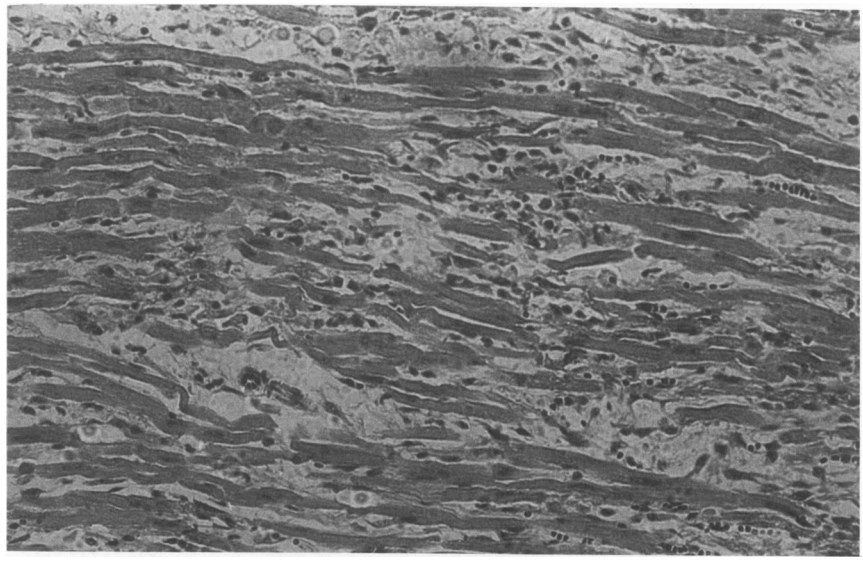

Figure 3—Myocarditis of chronic Chagas' disease in the rabbit. Notice lysis of heart myofibers in association with lymphocytic infiltrates. (H&E, ×160)

heart, skeletal muscles, and segments of the intestine of *T cruzi*-infected rabbits parallel those recorded in humans.

Usefulness of the Model

Chagas' disease affects millions of persons in Central and South America. The treatment available is far from satisfactory. There are indications that a vaccine against *T cruzi* may not be feasible by conventional means. Evidence in the literature indicates that autoimmunity may play a central role in the pathogenesis of Chagas' disease.[6-9] The availability of an animal model of the human disease appears, therefore, to be essential in the immunopathologic studies, immunoprophylaxis, and evaluation of the chemotherapeutic effects of drugs.

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