GEOGRAPHIC PATHOLOGY
CHRONIC MYOCARDITIS OF VENEZUELA

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Soon after his arrival in Caracas in 1936, Rudolf Jaffé[1] noted the frequent occurrence of an unusual form of chronic myocarditis of unknown etiology (chronic myocarditis of Venezuela or *miocarditis idiopatica venezolana*) which was a principal cause of death. This condition has also been reported from most of the other Latin-American countries[2] as an important leading cause of death.[3-5] The purpose of the present study was to review the clinical and pathologic features of this disorder in Venezuela and to derive, if possible, suggestions that might lead to an understanding of its etiology, and possibly to its control, prevention or eradication.

Method

Through the courtesy of Dr. José A. O'Daly, Professor of Pathology and Director of the Institute of Pathologic Anatomy of the Central University of Venezuela; Dr. Luis M. Carbonell, Professor of Pathology, Central University of Venezuela, and Dr. José I. Baldó, Chief, Department of Adult Hygiene and Chronic Diseases, Republic of Venezuela, arrangements were made to examine patients hospitalized with the disease. The opportunity was also provided to investigate the available pathologic material pertaining to chronic myocarditis at the Central University and in a number of hospitals in Venezuela. The pathologic material comprised the protocols and prepared slides in various departments of pathology, representative of approximately 100 cases, and fresh tissue from 6 necropsies. Available blocks of myocardial tissue were sectioned and stained with the hematoxylin and eosin, van Gieson, and orcein stains.

Clinical Features

This form of chronic myocarditis in Venezuela affects principally persons of poor economic status from rural areas. Many patients come

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from regions in which Chagas' disease is endemic or give a history of having had the disease. The average age of 42 patients with chronic myocarditis at Vargas Hospital, Caracas, studied by Bruni Celli,[6] was 44 years (range of ages, 18 to 77 years). Most of the patients with the disorder in Valencia, upon whom Brass[7] performed necropsies, were in the fourth or fifth decades of life, a lesser percentage in the sixth or seventh decades.

The disease may cause sudden, unexpected death while the person is at work or walking in the street. More often the patient has one or more episodes of congestive heart failure which, if uncomplicated, generally improve with rest in bed.[8] The failure may last several weeks or months but is likely to recur. The patient's blood pressure is generally normal but may be either mildly elevated or, more often, depressed. On radiologic examination, the outlines of all the chambers of the heart are seen to be greatly enlarged, and the lungs are congested; the enlargement of the left atrium resembles that seen in mitral stenosis. Among the disturbances of conduction revealed by the electrocardiogram are bradycardia, paroxysmal tachycardia, multicentric ventricular extrasystoles, bundle branch block (more commonly of the right bundle), and sometimes atrial fibrillation.

Maekelt[9] found the complement-fixation (Machado-Guerreiro) test to be positive in as many as 60 per cent of patients with chronic myocarditis in Valencia; among 381 persons at necropsy, he found positive reactions in 76 per cent of those with chronic myocarditis, and in only 5 per cent of those who did not have this condition.

Xenodiagnosis with the triatomid insect, *Rhodnius prolixus* (the carrier of Chagas' disease in Venezuela), has been found to be positive in as many as 80 per cent of the patients.[7] If the method of xenodiagnosis is employed, care must be taken to distinguish the crithidial forms of *Trypanosoma cruzi* from those of *Trypanosoma rangeli,* a nonpathogenic organism which in Venezuela may affect man and animals, as well as the *Rhodnius prolixus*.[10,11] In the chronic phase of experimental Chagas' disease in guinea pigs and puppies, Pifano[12] found positive xenodiagnosis in 65 per cent of examinations when the insect was given one blood meal, and in 85 per cent of examinations when the insect was given two meals. From his analysis of the findings in clinical cases, he concluded[13] that approximately 60 per cent of patients with chronic myocarditis gave a positive xenodiagnosis after a single test and about 80 per cent gave a positive result after two tests, if an interval of 2 or 3 weeks was allowed between the two blood meals. At the Vargas Hospital, Bruni Celli[6] noted that 50 per cent of patients with chronic myocarditis had positive xenodiagnosis while 70 per cent of those with positive xeno-

diagnosis had chronic myocarditis. A series of 96 patients were given a total of 123 xenodiagnostic tests; among 42 with chronic myocarditis, 21 (50 per cent) had a positive xenodiagnosis, while of 54 patients who did not have chronic myocarditis, only 9 gave a positive finding (16.7 per cent).

A precipitin reaction[14] has not been used extensively. Blood culture and inoculation of blood into laboratory animals (white mice) for recovery of parasites, while helpful in acute Chagas' disease, are not of value in this form of chronic myocarditis.

Pathologic Observations

Coronary arterial atherosclerosis, which is uncommon in the rural areas of Venezuela,[8] is generally absent or mild among patients with chronic myocarditis from the rural areas near Valencia.[7] Pericardial fluid may be increased (1,500 ml. in one reported instance[15]), and occasionally is serohemorrhagic. Gross evidence of pericarditis may be mild, but is usually absent.

The following represent the principal gross and microscopic features in our cases.

Gross Features

The usual cause of death was congestive heart failure. No evidence was present of hypertension or of coronary, valvular, renal or other diseases. The heart was moderately or greatly enlarged, globose, flabby, and had a dull, lusterless appearance. The weight of the heart generally ranged between 400 and 700 gm. (Köberle[16] reported weights of 1,000 gm. and over.) The musculature was turbid and occasionally exhibited focal scarring. All of the chambers were enlarged, and the region of the pulmonary "conus" was frequently dilated. The dilatation of all the chambers was often extreme and usually greater than the degree of hypertrophy. The wall of the left ventricle in the apical region, and at times the subvalvular region of the posterior wall, was thin and showed early aneurysmal dilatation on occasion[17]; these locations and the right atrium and atrial appendage were also preferred sites for thrombosis and subendocardial fibrosis. The mural thrombi of the right side of the heart frequently gave rise to pulmonary emboli; less often, thrombi in the left cardiac chambers yielded renal, splenic, cerebral or other emboli. Often petechial or larger hemorrhages were present in the epicardium or beneath the endocardium, particularly of the right atrium, and occasionally hemorrhage was present in the subendocardial region at the base of the ventricular septum on the left ventricular aspect. Thrombi or scarring of the myocardium or endocardium appeared in any chamber; the

ventricular septum and the ventricles often were severely involved, particularly the apical portions and the papillary muscles. Fibrosis was patchy and scattered but might also be severe and fairly diffuse in a given area.

Microscopic Features

The epicardium often contained focal collections of lymphocytes. A striking feature was the diffuse and heavy infiltration of the myocardium (Fig. 1) with lymphocytes, and, not infrequently, with histiocytes. The cellular infiltrations might be focal or perivascular, but the arteries and arterioles showed no lesions. Some plasma cells, eosinophils or neutrophils were present in certain instances. Occasionally, granulomatous lesions were prominent and were characterized by areas of necrosis and few giant cells. The most constant and conspicuous features were severe passive hyperemia and interstitial edema (Fig. 2). The inflammatory exudate usually affected the walls of all chambers. Many myocardial fibers showed hydropic or fatty alterations, necrosis (Figs. 3 and 4), atrophy (Fig. 5), or compensatory hypertrophy with large or hyperchromatic or pyknotic nuclei (Fig. 6). Often there seemed to be little or no new connective tissue at the sites of recent destruction of myofibers. Later in the course of the disease, fibrous connective tissue was found chiefly in the subendocardial region and the inner third of the myocardium, focally or over wide areas. Foci of subendocardial fibrosis represented old organized mural thrombi in some instances, and fresh or organizing mural thrombi commonly were present. Capillaries or small veins were occasionally occluded by fibrinous thrombi (Fig. 7) which led to focal fibrosis or microscopic infarcts. A characteristic feature of the myocarditis was the diffuse fine fibrosis (Fig. 8) which differed from the usual appearance of "hypoxemic" fibrosis.[18] Focal areas of calcification (Fig. 9) were found in association with necrosis or fibrosis. Rarely, a leishmanial pseudocyst was found within a myocardial fiber.

Discussion

Concepts Concerning This Form of Chronic Myocarditis

Jaffé[1] reported an incidence of 18 per cent of chronic myocarditis at necropsy (between 1936 and 1944) at the Vargas Hospital in Caracas. In about two thirds of the cases so affected, the cardiac lesion was the cause of death. In 450 necropsies he found microscopic evidence of myocarditis which was often associated with syphilis, schistosomiasis or ancylostomiasis. He believed that these infectious processes produced injury and degeneration of the myocardial fibers and that the absorbed necrotic muscle tissue served as a sensitizing substance[19] which caused

an inflammatory reaction when myocardial tissue was subsequently destroyed by these or other agents or their products, whether present in the heart or other organs of the body. He also thought that the allergic mechanism resulted from parenchymal damage to myocardial fibers, owing to nutritional deficiency or absence of vitamin B_1 in the diet.[20-22] Gil Yépez[23] felt that the myocarditis of Venezuela was related to parasitism and nutritional factors.

Laranja, Dias, Nobrega and Miranda[2] believed that this form of chronic myocarditis represented a chronic stage of Chagas' disease. Triatomid insect vectors of Chagas' disease are distributed over an area extending from the southern part of the United States to Argentina.[2] These workers thought that acute Chagas' disease, which occurs predominantly in infancy and childhood and from which most patients recover after a number of months, gradually evolves as the chronic form of Chagas' heart disease, and that these patients may remain infected for the rest of their lives. While recognizing that this etiology is not proved, Pifano,[11-13] Brass[7] and others[3-5,16,24] also favor the concept that chronic myocarditis is a chronic phase of Chagas' disease. In a number of instances[2,16] one or a few leishmanial pseudocysts have been found upon examination of hundreds of serial sections of myocardium of patients with chronic myocarditis. In one of our cases a number of sections contained pseudocysts, and in a second instance a single section contained pseudocysts.

Tejada and Castro[5] encountered 44 cases of chronic myocarditis among 800 necropsies in Guatemala. The chronic myocarditis, which was by far the commonest form of heart disease in Guatemala, was similar in type to that reported from Venezuela and other Latin-American countries. Because of the absence of parasites from myocardial fibers despite intense diffuse interstitial inflammation, and because most patients with myocarditis came from areas in which Chagas' disease was endemic, Tejada and Castro accepted the hypothesis of Jaffé that the myocarditis was allergic in nature. They explained the myocarditis by recurrent infection with the organism of Chagas' disease. As a result of an initial acute attack of Chagas' disease, some myocardial fibers were thought to have degenerated and become sensitized. Auto-antibodies were released from the sensitized myofibers when the patient was subsequently reinfected with *Trypanosoma cruzi*, thus initiating the allergic reaction. Their idea differed from the concept of Jaffé who did not accept Chagas' disease as the cause of the myocarditis.

Brass,[18] on the basis of material in Valencia, attributed death to chronic myocarditis in 43 per cent of adults who came to necropsy, exclusive of those who died from accidental or unnatural causes. Myo-

carditis was most frequent between the ages of 30 and 60 years. The majority of patients affected were poor farm workers and laborers from regions south and southwest of Valencia, while relatively few of those who lived in Valencia suffered from the disorder. In the gross examination of the heart, he often found dilatation of the pulmonary conus, sometimes aneurysm of the left ventricle, especially at the apex, no evidence of pericarditis, and patchy fibrosis of the muscle, which was more easily recognizable in formalin-fixed tissue. Microscopically, the features were those of a nonspecific chronic myocarditis, chiefly with lymphocytic infiltration. About 10 per cent of the cases had granulomatous lesions, areas of necrosis, and occasionally foreign body giant cells. Brass found no statistical relationship to syphilis, schistosomiasis, or undernutrition. Of 182 patients from the zone east of Valencia where bilharziasis was endemic, at necropsy 32 per cent had bilharziasis and 25 per cent had chronic myocarditis; of 138 patients from the zone west of the city, only 0.5 per cent had bilharziasis and 24 per cent had chronic myocarditis; and of 370 patients from the zone south of Valencia, none had bilharziasis and 50 per cent had chronic myocarditis. Brass believed that the method of xenodiagnosis might furnish presumptive evidence, but that it did not constitute proof that the chronic myocarditis was the result of Chagas' disease. He found no evidence of nutritional deficiency to suggest that the myocarditis was related to dietary insufficiency.

Salfelder[25] stated that he had seen only about 25 examples of idiopathic chronic myocarditis in 1,400 necropsies (1.8 per cent) in Merida, Venezuela (situated in the Andes region, 30 miles south of Lake Maracaibo), and in none of these 25 cases was he able to find leishmanias in the myocardium. He believed that this form of chronic myocarditis had no relation to syphilis, that a relationship to Necator infestation was improbable, and that bilharziasis was not a factor since it did not occur in this locality. Salfelder thought that Chagas' disease might possibly be the basis of the infection, since most of his patients had positive xenodiagnosis. Most of the patients with chronic myocarditis were not cachectic, and he did not regard malnutrition as a factor.

Köberle[16] investigated 100 cases of chronic myocarditis at necropsy. Among the first 50 cases, in each of which as many as 500 serial sections of heart muscle were examined, he found 18 with leishmanial pseudocysts in myocardial fibers. He noted inflammatory cell involvement of the cardiac ganglia and conduction system (sinus node, bundle of His and bundle branches) with destruction of cells or fibers and replacement by fibrous tissue. This was felt to explain the excessive dilatation and hypertrophy of the heart, particularly of the right atrium and right ventricle. Köberle designated this form of cardiac hypertrophy as

"neurogenic." He believed that the chronic myocarditis represented chronic Chagas' disease.

Distinction from Certain Other Forms of Chronic Myocarditis

Dietary Insufficiency. Toreson [26] reported diffuse isolated myocarditis at necropsy in a 15-year-old girl with a long history of dietary insufficiency and malnutrition. The heart weighed 295 gm., the ventricles were hypertrophic, small mural thrombi were present in all chambers, the myocardium was gray-brown, mottled and soft, and showed fibrosis. The myocardial lesions consisted of widespread and irregular hydropic degeneration of muscle fibers, small focal areas of acute inflammation with pronounced exudation of neutrophils, severe edema, hyperemia, and some necrosis of muscle fibers. There were also atrophy and hypertrophy of myocardial fibers as well as replacement by dense collagenous tissue.

Generally, vitamin deficiency is attended by little or no inflammatory infiltration in the myocardium. In beriberi heart disease, the heart is enlarged, but the myocardial alterations are nonspecific, with hydropic degeneration of muscle fibers and interstitial edema.[27,28] Follis [29] stated that in beriberi the heart is reported to be grossly dilated, sometimes hypertrophied, and microscopically to have hydropic degeneration, mild scarring and fatty degeneration. Follis [30] also stated that the anatomic cardiac features in beriberi are equivocal; he noted the complete lack of any consistent pathognomonic lesion at necropsy. An instance of prolonged myocardial disease attributed to beriberi, observed intermittently over a period of 18 years, was reported by Jervey [31] in a 33-year-old Negro woman who drank alcohol excessively and had a deficient diet. Her heart weighed 530 gm., all chambers were dilated, and the ventricles were hypertrophic. The microscopic lesions included interstitial edema, fine fibrosis, some endocardial fibroelastic thickening, but only a rare interstitial collection of leukocytes.

In pigs dying with thiamine deficiency, Follis, Miller, Wintrobe and Stein [32] found cardiac dilatation without hypertrophy, and focal and diffuse myocardial necrosis. In animals that had several episodes of severe thiamine deficiency, scars were present at the sites of healed necrotic lesions. In rats and hogs with deficiency of both vitamin B and potassium, Thomas, Mylon and Winternitz [33] found pronounced cellular infiltration, chiefly of mononuclear cells, in addition to necrosis of muscle fibers.

Sensitization Produced by Drugs. The myocarditis associated with sulfonamide sensitivity [34,35] is attended by focal paravascular or diffuse infiltrations of acidophilic histiocytes with a variable number of other mononuclear cells, both neutrophils and eosinophils. Epinephrine [36] and

l-norepinephrine[37] are other commonly used drugs which may produce myocarditis.

Infectious Diseases. Myocarditis is found most often in association with infectious diseases.[38] In a study of tissue reactions in fatal cases of *Streptococcus hemolyticus* infection, Mallory and Keefer[39] found cardiac lesions in 46 of 79 cases (57 per cent), generally in the form of focal accumulation of cells, mainly lymphocytes and plasma cells, but sometimes neutrophils and eosinophils. They believed that the acute type of lesion with neutrophilic leukocytes may have been induced by localization of bacteria, and that the mononuclear reaction represented a later healing phase of the lesion. The myocarditis, however, was generally focal and typically subendocardial rather than diffuse.

In diphtheria, the "myocarditis" represents part of a reparative process, and fibrosis follows necrosis and destruction of muscle fibers by the diphtheria toxin. Interstitial edema and interstitial infiltration with inflammatory cells may be absent. Gore and Saphir[40] found serous myocarditis in 10 per cent of 160 patients who had had acute or subacute glomerulonephritis; in the affected hearts, the most prominent feature was interstitial accumulation of fluid while the cellular components, chiefly lymphocytes and histiocytes (endothelial leukocytes), were relatively sparse.

Viral Diseases. Myocarditis of nonspecific type has been described in association with a variety of viral affections, such as viral pneumonia, poliomyelitis, and Coxsackie virus infection. Spain, Bradess and Parsonnet[41] reported a patient who died of poliomyelitis after an illness of 2 days with acute myocarditis characterized by interstitial edema, fibrin, focal myocardial necrosis, and focal and diffuse collections of neutrophils and lymphocytes. In 2 patients, each of whom died of poliomyelitis after an illness of 22 days, there was considerable myocardial fibrosis and cellular infiltration consisting principally of lymphocytes. Similarly, Saphir[42] noted, in patients who died of poliomyelitis during the first week of infection, that the myocardium was heavily, and sometimes massively, invaded by neutrophils while in those who died 4 to 6 weeks after the onset of the ailment, the myocardium contained many lymphocytes and monocytes. Ludden and Edwards,[43] in a study of 14 cases of myocarditis associated with poliomyelitis, pointed out the presence of muscular degeneration which included swelling of fibers, loss of striations, cytoplasmic vacuolation, fragmentation, karyolysis, and complete focal necrosis of muscle fibers with irregular staining and disorganized masses of coagulated cytoplasm. These features were present in addition to infiltration of inflammatory cells. Saphir[44] and his associates[45,46] have stated that in various forms of viral myocarditis, in addition to the inter-

stitial exudate, necrosis of isolated fibers or groups of muscle fibers invariably occurs.

Schmidt[47] experimentally produced viral myocarditis in laboratory animals (mice, guinea pigs, and hamsters). In mice, 6 days after infection, the myocardium exhibited small necrotic foci with interstitial monocytic infiltration of surrounding areas, and edema; at 9 days, necrosis was more extensive and fibroblasts began to appear, and these were present in increasing numbers on the eleventh or twelfth day. Calcification was manifest as early as 10 days and was common after the twelfth or 13th day. At 20 days both fibrosis and calcification were present.

Javett and associates[48] investigated an outbreak of acute Coxsackie group B virus infection affecting 10 newborn babies in a maternity home. Six of the babies died of circulatory collapse, and necropsies were performed in 3 cases. In these the heart showed patchy interstitial edema, pleomorphic cellular infiltrations (patchy in 2 and diffuse in 1) with the heaviest involvement in the inner third of the myocardium. The infiltrates consisted of many large mononuclear cells with vesicular nuclei, some with vacuolated cytoplasm, a moderate number of histiocytes with basophilic cytoplasm, a few lymphocytes, and occasional neutrophils, eosinophils, and plasma cells. Fibroblasts were not observed. The muscle fibers contained areas in which the affinity for Heidenhain's hematoxylin stain was lost. Eventually the transverse striations also were lost, and the muscle fibers disintegrated, leaving behind empty sarcolemmal sheaths. The authors believed that the cellular infiltration preceded the changes in the muscle fibers.

Rickettsial Disease. In various rickettsial infections, including scrub typhus (tsutsugamushi disease), epidemic typhus and Rocky mountain spotted fever, Allen and Spitz[49] noted an apparent state of preservation of myocardial fibers despite intense interstitial inflammatory infiltration. In the exudates, plasma cells, acidophilic macrophages or Anitschkow myocytes predominated. In addition, arterial or periarterial lesions were often present, both in the heart and in many other organs of the body.

Parasitic Infections. Recognition of the parasite in the myocardium and usually also elsewhere in the body is generally necessary for diagnosis. In trichinosis[50] the myocardial lesions were usually focal, and the endocardium and epicardium might also be affected. Occasionally, transient larvae were found, but larvae never encysted in the myocardium. The infiltrations were often granulomatous, with histiocytes predominating, and with lesser numbers of neutrophils, eosinophils, lymphocytes and macrophages, and sometimes plasma cells. A few muscle fibers

were necrotic, and healing occurred with fine fibrosis but without sizable scars.

In toxoplasmosis, the central nervous system and the myocardium were chiefly involved. Pseudocysts in the myocardial fibers were often unassociated with inflammation. The infiltrate, which was likely to be present at some distance from parasitized fibers, was composed of focal coagulative necrosis of muscle, neutrophils, eosinophils and mononuclear cells.[51]

Acute Chagas' disease is a clear-cut entity. It affects children primarily but may be encountered at any age, and most often occurs among persons who live in rural areas in huts having palm-leaf covered roofs in which are sheltered the *Rhodnius prolixus,* a nocturnal blood-sucking triatomid insect. Generally a history is obtained that the patient was bitten by the insect, particularly about the face, and that he subsequently had swelling or ulceration of the affected area (chagoma) and regional lymphadenitis (bubo); often *T. cruzi* is recovered from the blood by culture or after animal inoculation, and the xenodiagnosis and complement-fixation tests are positive. Electrocardiographic changes, including disturbances of conduction, are common. Radiologically, all chambers of the heart are generally greatly enlarged. At necropsy the cardiac chambers are greatly dilated, the muscle is pale, mottled and flabby. Microscopically, cystlike accumulations of leishmanias are present in muscle fibers (Fig. 10), and they usually are not surrounded by inflammatory cells. The infiltrates usually occur near the parasitized muscle fibers and consist of lymphocytes, plasma cells, eosinophils, macrophages and occasionally neutrophils. Infiltrations may be focal but are often diffuse and extremely severe.

Enos and Elton[52] reported one instance of fatal acute Chagas' disease in an 18-year-old white North American soldier stationed in the Panama Canal Zone; he had been on guard duty in a forested area. Brass[7] encountered acute infection chiefly in children. In acute human infection with clinical evidences of cardiac insufficiency, many myocardial fibers contained parasites, and the heart was heavily infiltrated with inflammatory cells but was not scarred. In his experiments with white mice, Brass found that leishmanias were most abundant in the heart during the fourth week; the organisms began to disappear during the sixth or seventh week and had virtually disappeared after about 3 months even though inflammatory cells persisted.

Clinically, chronic myocarditis of Venezuela was recognizable by the occurrence of congestive failure without known etiology, by massive dilatation of the heart without accompanying hypertension, and by frequent electrocardiographic conduction disturbances. Pathologically

also, the gross and microscopic features were distinctive although not specific. The epidemiologic and serologic features and the occasional observations of leishmanias in myocardial fibers all suggested an association with Chagas' disease.

Because of the frequent association of bilharziasis, necatoriasis and syphilis, Jaffé [1] suspected that these diseases were factors in the production of the myocarditis. He believed that as a result of any of a variety of conditions, including hypovitaminosis or avitaminosis B_1, myocardial fibers were injured and became sensitized to the products of myocardial degeneration which might be induced by any agent subsequently. Bilharziasis, necatoriasis and syphilis seldom produce myocardial damage by direct invasion of the causative organism, and it seems doubtful that any of these organisms produces a toxin that affects the heart. In many countries where these conditions are common, this form of chronic myocarditis is rare or absent. Moreover, the myocarditis occurs frequently among individuals who do not have any of these diseases or who come from areas in which bilharziasis and necatoriasis are absent or rare. The assumption that the myocarditis is related to hypovitaminosis or avitaminosis B_1 does not have clinical, experimental or pathologic support. Neither can it be regarded as a form of beriberi since in the latter condition the heart shows little or no inflammatory cell infiltration. While it is possible that deficiency of vitamin B_1 or deficiency of a combination of elements in the diet may be related to the chronic myocarditis, the evidence at hand is not convincing.

On the other hand, much weight must be given to the hypothesis that the cardiac inflammatory change may represent an allergic reaction. Although Jaffé [20] denied that Chagas' disease played any important role in the production of this form of myocarditis, his hypothesis nevertheless admitted the possibility that the lesion could result from recurrent infection with the trypanosome. Thus any one of many agents could sensitize the myocardium so that subsequent damage would release autoantibodies and induce an inflammatory reaction in the heart. However, if this were the case, the same type of chronic myocarditis should occur with great frequency in European countries and in the United States. Probably the specific factor or agent operative in the production of this form of myocarditis does not commonly occur in Europe or the United States.

The great majority of investigators in Venezuela and in other Latin-American countries, who have studied this problem, tend to regard the myocarditis as a chronic or recurrent phase of Chagas' disease. Much presumptive evidence exists to support this point of view: (1) The disease is common in localities in which acute Chagas' disease is endemic,

and rare or absent in areas in which it is absent. (2) Although acute Chagas' disease primarily affects children, chronic myocarditis is seen in adults, many of whom give a history of having had acute Chagas' disease. (3) The clinical, radiologic, and electrocardiographic features with respect to the heart are remarkably similar to those seen in acute Chagas' disease. (4) The frequent positive findings with the complement-fixation test for Chagas' disease, and the method of xenodiagnosis are suggestive evidence. (5) Pathologically, the gross alterations (except for scarring) and the microscopic lesions (except for the rarity of leishmanial pseudocysts in myocardial fibers) are similar to those of acute Chagas' disease.

During recent years, the incidence of chronic myocarditis appears to have diminished in the hospitals of Caracas. This decline is attributed [8] principally to expansion and improvement of hospital facilities in the rural areas, so that most patients now enter the local hospitals instead of going to the capital for treatment. The disease is largely absent among inhabitants of metropolitan Caracas. According to figures released by the Ministry of Health in July 1958, approximately 3,100,000 persons, or one half the population of Venezuela, live in rural conditions.[8]

The thought naturally occurs that the lesion might be viral in nature. The microscopic lesions, while nonspecific, resemble those seen in a number of virus diseases of the heart. The prominent interstitial edema, the character of the inflammatory infiltrate, and particularly the destruction of myocardial fibers, all are compatible with reactions produced by viruses. No reports of attempts to recover a virus from the myocardium of these patients have been encountered. It would appear worth while to examine the myocardium for the presence of a virus as an independent agent or as an agent associated with Chagas' disease.

On the assumption that the infection may represent a chronic form of Chagas' disease, Brass [7] believed that the huts in endemic areas should be sprayed twice a year, allowing an interval of about 4 weeks, since at the time of the first spraying the eggs of the insect vectors might be well hidden and thus not affected, while a second spraying after 4 weeks would probably destroy the new larvae. DDT is said not to affect the *Rhodnius prolixus* but destroys ants which are natural enemies of the triatomids.* Salfelder [25] stated that in the further investigations of the disease, it was of primary importance to establish a laboratory well equipped for bacteriology, serology, and parasitology, with expert personnel, in the region where Chagas' disease was apparently most common (Valencia).

* One of the newer effective sprays is Dieldrin, a chlorinated hydrocarbon insecticide (manufactured by Shell Chemical Corporation, Agricultural Chemicals Division, 460 Park Ave., New York 22, N.Y.).

"Chronic myocarditis of Venezuela" appears to be identical with a form of chronic myocarditis that is endemic, frequent, and of serious public health significance in most Latin-American countries. It would appear, therefore, advisable to consider the clinical, pathologic, and epidemiologic aspects of this disease in its international framework. In this fashion there could be formulated measures for prophylaxis, treatment, experimental study, and control.

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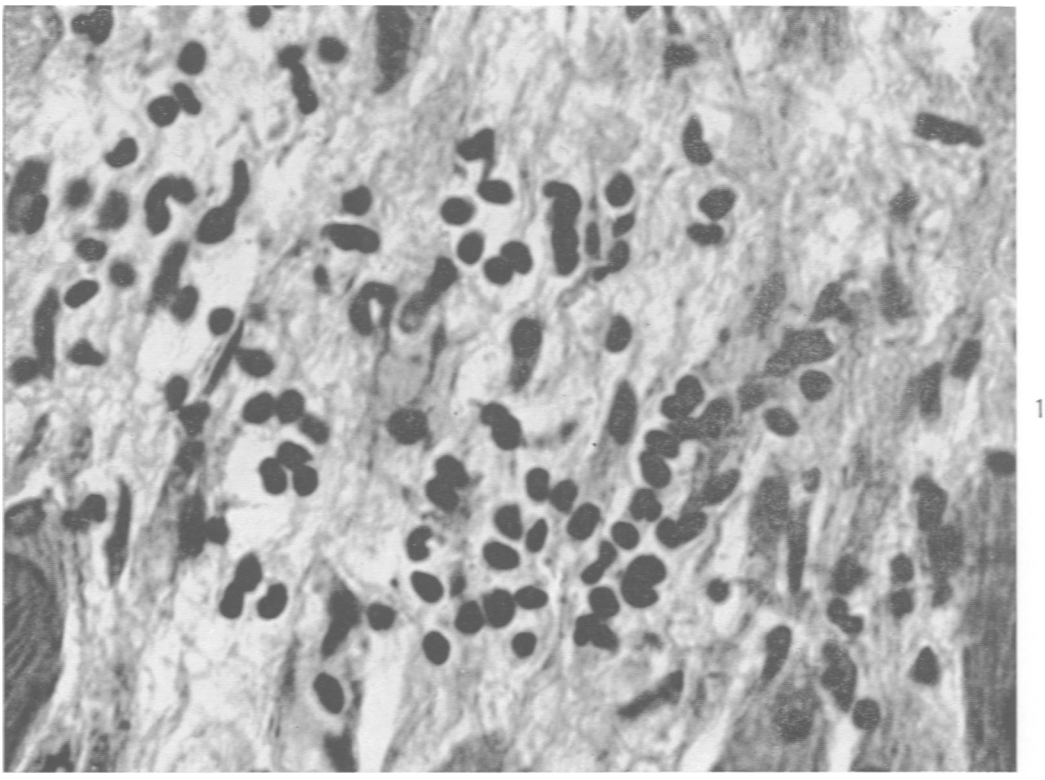
[*Illustrations follow*]

Legends for Figures

Photomicrographs were prepared from sections stained with hematoxylin and eosin.

Fig. 1. (Case 10581, Vargas Hospital, Dr. Bruni Celli.) A 32-year-old woman with congestive heart failure provided a history of having been bitten by a triatomid insect. The complement-fixation test for Chagas' disease was negative. At necropsy there were hydropericardium and bilateral hydrothorax; the heart weighed 650 gm. The myocardium exhibits degeneration or disappearance of myofibers. A serous exudate contains lymphocytes and histiocytes. × 400 (enlarged 1½ times).

Fig. 2. (59B63, 59P103. Case 2110, Children's Hospital, Dr. Lozano.) Chronic myocarditis in a child. Note interstitial edema, hydropic degeneration and disintegration of muscle fibers. × 825.



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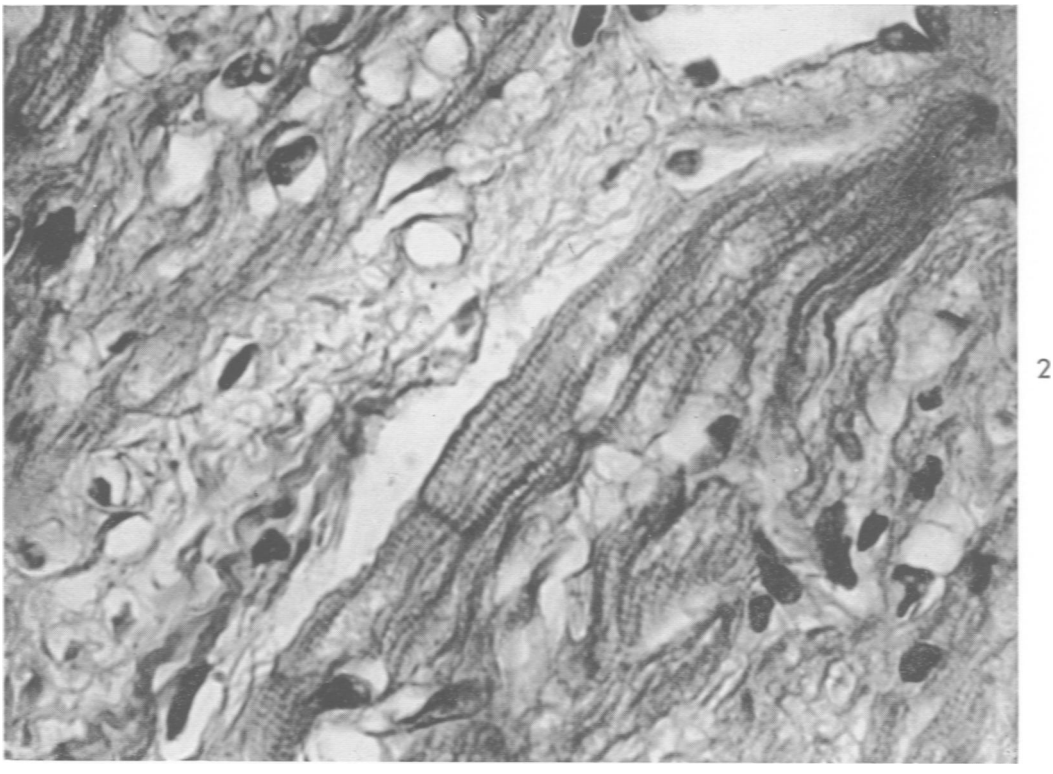

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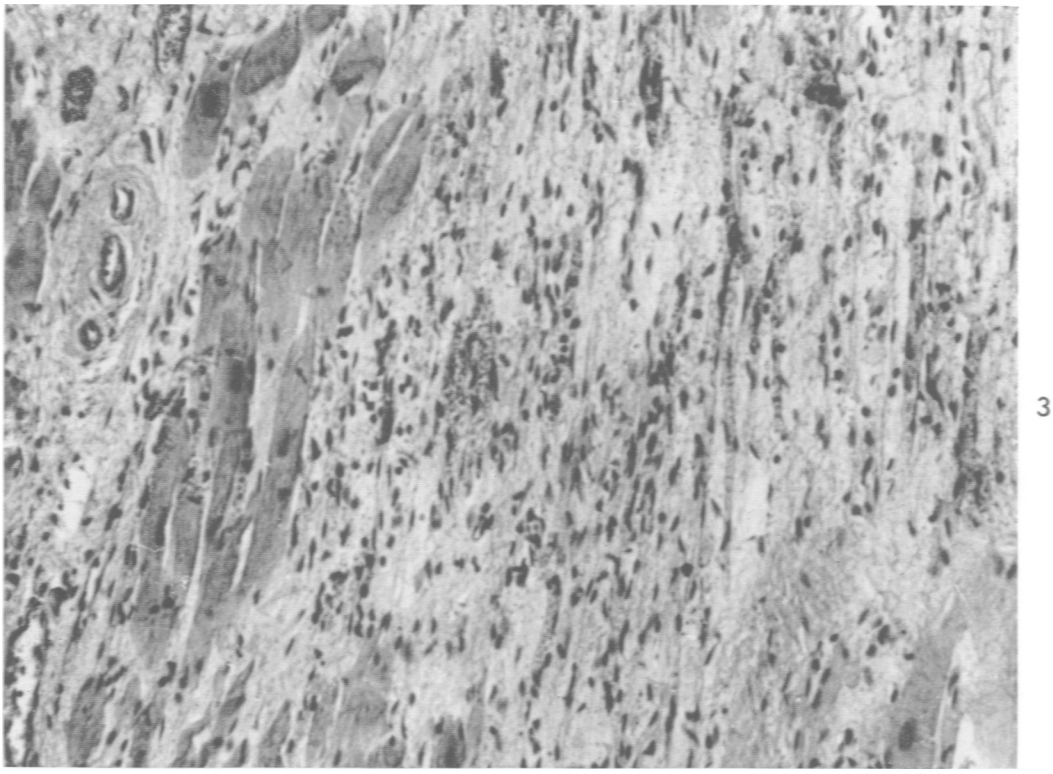
FIG. 3. (Case illustrated in Fig. 1.) Severe degeneration of muscle fibers is accompanied by edema, hyperemia, infiltration with lymphocytes and histiocytes, and some collagenization. There is atrophy of some muscle fibers and hypertrophy of others. × 100 (enlarged 1½ times).

FIG. 4. (Case 10255, Vargas Hospital.) Left ventricle. There is interstitial edema and interruption and loss of some myocardial fibers. Hypertrophy appears in others. Note also the characteristic patchy fine fibrosis. A few collagen fibers are evident. × 100 (enlarged 1½ times).



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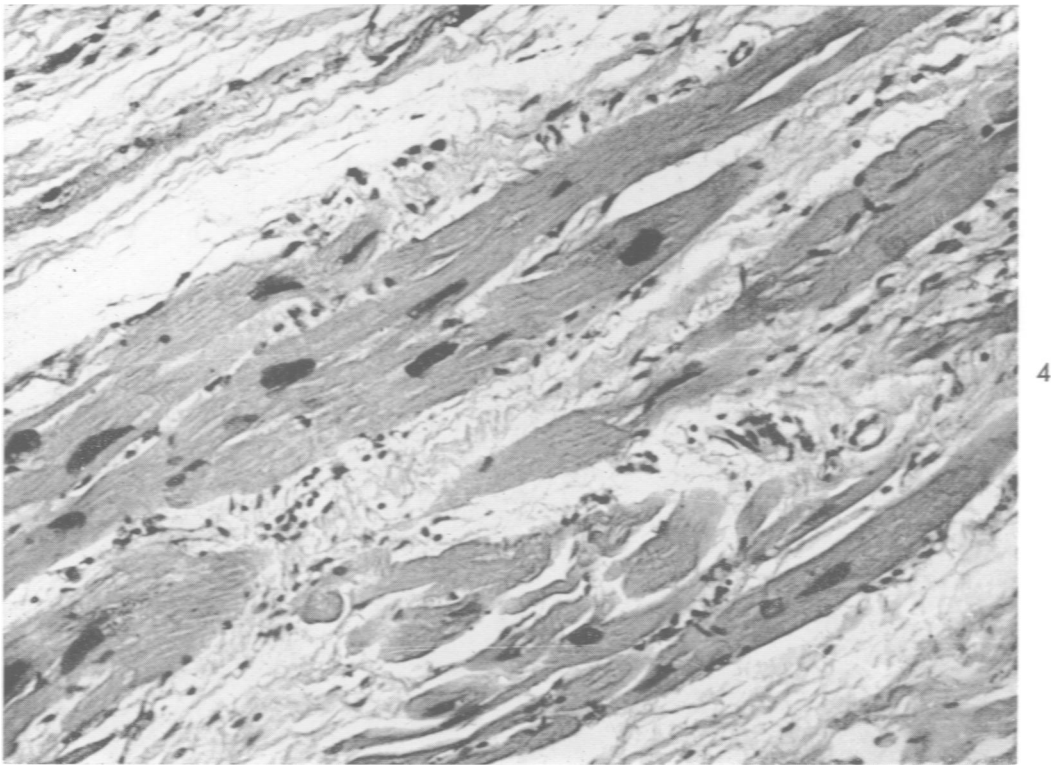

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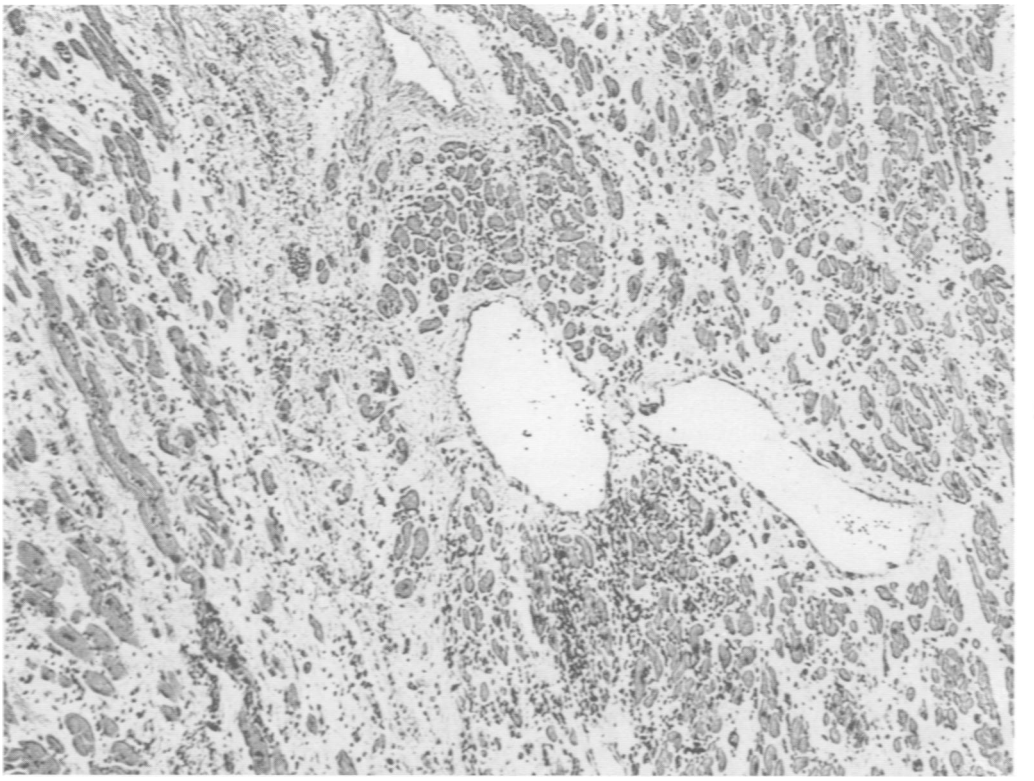
FIG. 5. (Case illustrated in Fig. 1.) Right ventricle. Note focal and scattered lymphocytic infiltrate, dilated capillaries, diffuse edema, atrophy of muscle fibers and, in the left portion of the field, patchy fibrosis. × 30 (enlarged 1½ times).

FIG. 6. (59B67. Case 10512, Vargas Hospital.) A 40-year-old man with a history of Chagas' disease died of congestive failure. Hydrothorax and ascites were present. The heart weighed 700 gm., and all chambers were enlarged ("global dilatation"). The left ventricle contained mural thrombi, and a recent thrombus was present in the right atrium. Focal active chronic inflammation is associated with hyperemia, interstitial edema, hydropic degeneration of muscle fibers, and occasional hypertrophic muscle fibers. × 100 (enlarged 1½ times).



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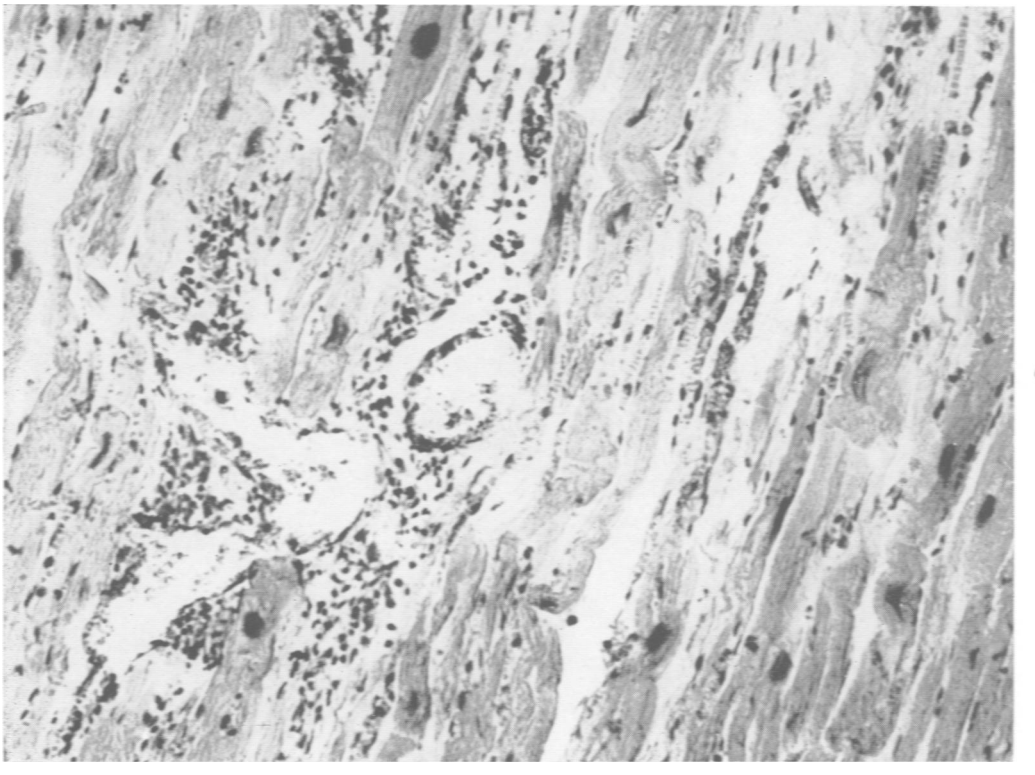

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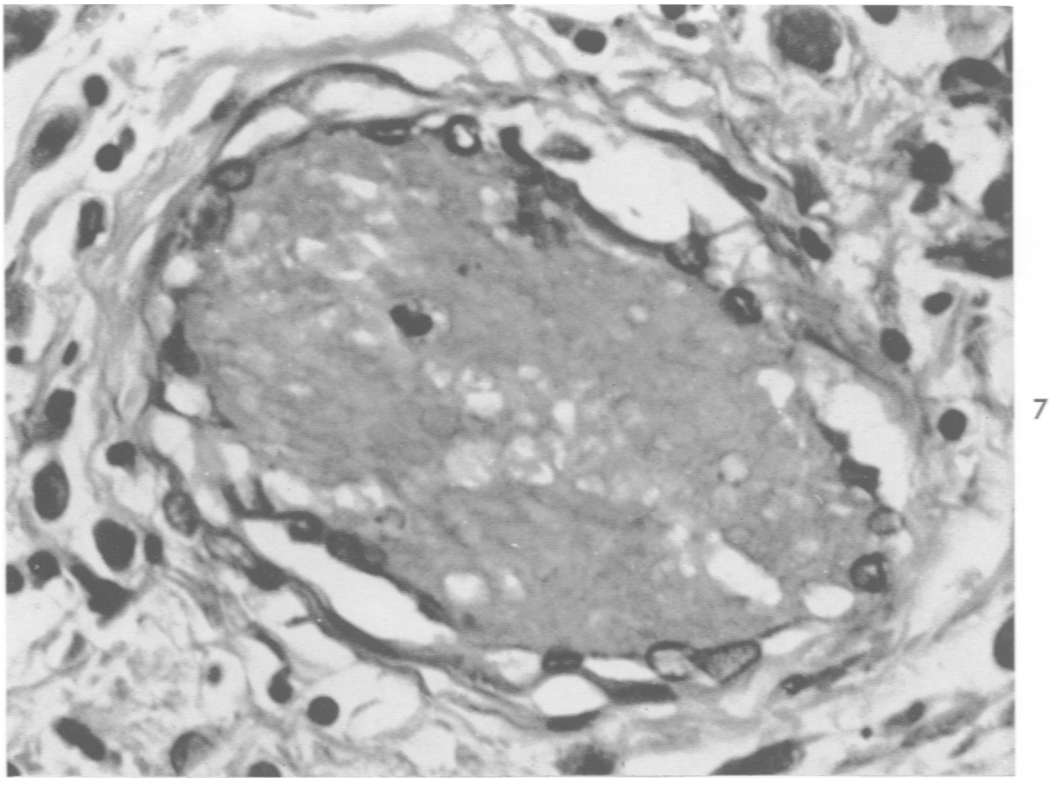
FIG. 7. (Case 9704, Vargas Hospital.) A recent capillary thrombus is shown. There is irregularity, swelling and apparent discontinuity of the capillary wall, and serous exudate around the capillary. × 400 (enlarged 1½ times).

FIG. 8. (A30-59, Central Hospital, Valencia, Dr. Brass.) A 28-year-old man from an area in which Chagas' disease was endemic died suddenly. The heart weighed 440 gm. and had a small aneurysm at the apex of the left ventricle. Extensive patchy fine fibrous connective tissue is frequent in this type of myocarditis. × 160.



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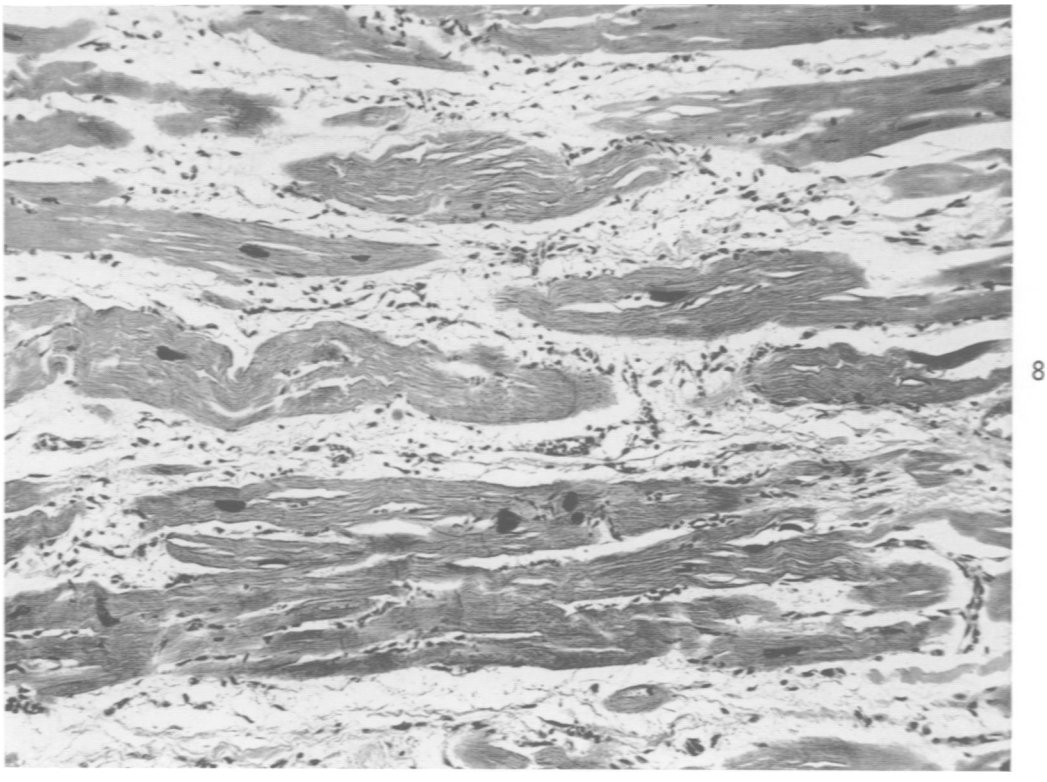

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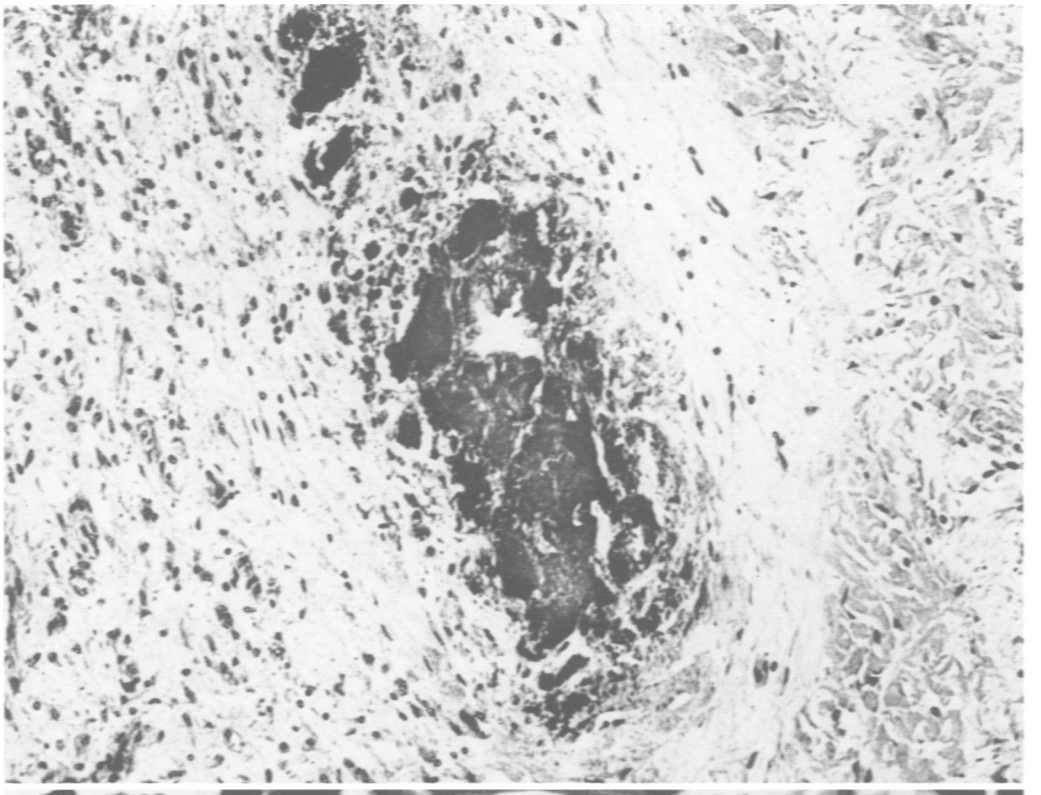
FIG. 9. (Same case as illustrated in Fig. 1.) An area of calcification and edema appears in the center. There is hyaline necrosis of muscle fibers at the right and infiltration with lymphocytes and histiocytes with beginning fibroblastic proliferation at the left. × 100 (enlarged 1½ times).

FIG. 10. (A152-59, Central Hospital, Valencia.) A 4-year-old girl from an endemic area of Chagas' disease, had a history of having been bitten by many triatomid insects. She died of acute chagasic myocarditis and encephalitis a few hours after admittance to the hospital. The heart weighed 130 gm. (normal weight, 72 gm.); all chambers were dilated, and the myocardium was pale. A leishmanial pseudocyst is evident in a myocardial fiber. Adjacent to it are edema and an infiltration, chiefly of lymphocytes and histiocytes. × 860.



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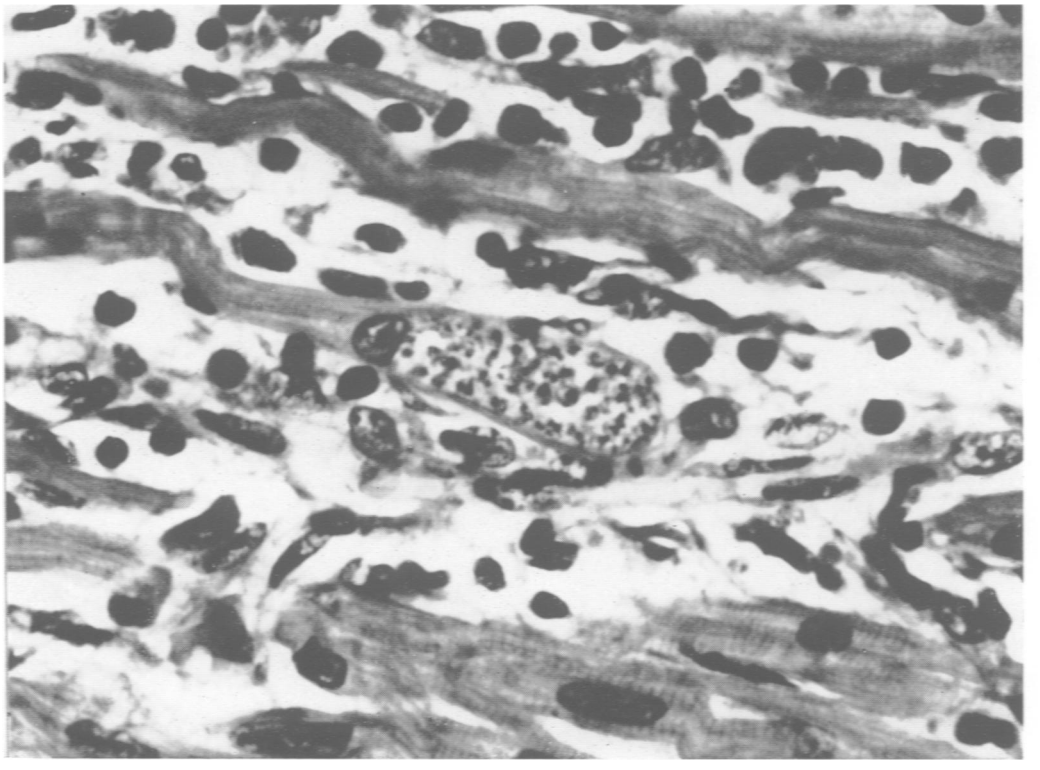

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