Experimental *Trypanosoma Cruzi* Myocarditis

Relative Effects Upon the Right and Left Ventricles

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In 1964 the characteristics and course of experimental heart disease in C3H mice produced by a strain of *Trypanosoma cruzi* (Colombian) were reported from this laboratory.[2] Although relatively mild initially, subsequent passages of the parasite have seen this experimental cardiomyopathy become increasingly severe both in the acute and the chronic phase.[3] In early passages congestive heart failure never occurred spontaneously but could be induced by certain interventions.[3-6] After the 100th passage heart failure could be observed consistently. For the first time, then, an experimental model of congestive heart failure of known natural cause became available for study. The present report characterizes this model, analyzes the relative involvement of the right and left ventricles, and discusses the implications for the pathogenesis of certain manifestations of Chagas' disease in man.

Material and Methods

Animals

Sixty weanling, 3-week-old and 48 adult, 18-week-old, male C3H mice (Jackson Laboratory) were used. The weanling mice were divided into 2 groups (I and II) of 30 each and the adult mice into 2 groups of 24 each (Groups III and IV). Groups I and III were infected with *T. cruzi*. The groups were so arranged that the average initial weight of weanling mice in each group was about 9.5 g, and of adult mice 23.8 g. Animals were housed 6 per cage (5 × 8 × 5 inches) and kept at a temperature of approximately 22° C. They were fed water and standard Purina rat chow *ad libitum*.

Origin, Inoculation, and Count of Parasites

T. cruzi (Colombian) was used for inoculation. The detailed passage history of this strain and the course of the acute myocarditis in C3H mice have been reported

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previously.[2] The strain of *T. cruzi* has been maintained in Harvard Swiss mice by monthly passages. After the hundredth and hundred-sixth passage in Harvard Swiss mice, the parasite was passed once through weanling C3H mice prior to use in weanling (Group I) and adult (Group III) mice in the present experiment.

The donor C3H mice were bled from the heart during peak parasitemia. Heparinized blood was diluted with saline, and motile trypanosomes were counted with a hemacytometer. Recipient mice were given inocula of 1000 organisms in 0.25 ml of saline intraperitoneally. Mice were weighed twice weekly. The degree of parasitemia was estimated semiquantitatively by counting 25 high-power fields (HPF) (× 430) of blood from the tail of all the inoculated animals at weekly intervals.

Necropsy Examination

Mice were checked twice daily for 70 days, then once daily. All dead mice were weighed and necropsied. Ten mice in Group I and 6 in Group III were cannibalized and could not be examined pathologically. Five mice from each group were sacrificed and necropsied on Day 84 after inoculation. The heart was severed 2 mm above the origin of the great vessels and, after removing blood by squeezing and blotting, was weighed to the nearest 1.0 mg, as were the liver and spleen (Precision Balance, D.S. Rollersmith). The entire heart, spleen, portions of right femur, lung, liver, colon, and skeletal muscle from the right leg were preserved in 10% buffered formalin.

All hearts were sectioned coronally from the base to the apex, into at least three separate pieces including both ventricles and atria. All sections were examined, as were portions of lung, colon, spleen, liver, and skeletal muscle. After paraffin embedding, the blocks were cut at 6 μ and stained with hematoxylin and eosin, as well as Masson-trichrome combined with elastic tissue stain. All measurements were taken on the central section, where the greatest extent of chamber dilatation and relative thickness of the ventricular walls was measured with an eyepiece chronometer. Multiple sections of heart and one section of skeletal muscle were examined for pseudocysts.

Analysis of Data

To study the course of the disease, Group I was subdivided. Group Ia included mice that died within 50 days of inoculation, in the acute parasitemic phase of the disease. Group Ib comprised the early subacute phase of disease from 51 to 84 days, and Group Ic the late subacute and chronic phase from 85 to 154 days.

Five age-matched control animals, not part of the experiment, were used for comparison with Group Ia. Five sacrificed animals from Group II served as age-matched controls for comparison with Groups Ib and Ic.

Since there was a significant difference in body weight between Groups I and II, and Groups III and IV, the organ weight/body weight ratios were used for comparisons. Heart weight/body weight ratio (HW/BW) has been validated for normal and starving rats by Beznak,[7] and for normal C3H mice from this laboratory by Elson and Abelmann.[4] Right ventricular dilatation index (RVDI) is:

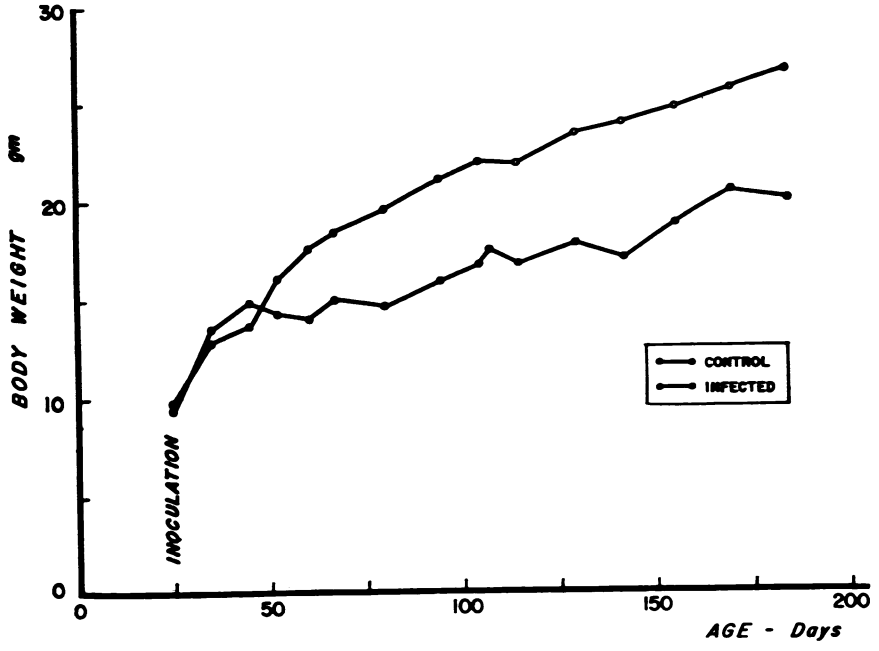
$$RVDI = \frac{\text{Thickness of right ventricular free wall (mm)}}{\text{Right ventricular cavity diameter (mm)}} \times 100$$

The severity of myocarditis and reactive fibrosis on histopathologic examination was graded on a 3-point scale: + indicated mild and focal lesions; ++ diffuse, mild or multiple, severe, focal lesions; and +++ diffuse and severe lesions.

Results

Weanling Mice (Groups I and II; Table 1)

Body Weight. At the age of 22 days, the mean body weight was 9.5 g in Groups I (infected) and II (control). On Day 42, Group I weighed 14.9 g, significantly more than Group II at 13.6 g. However, from Day 52 to Day 160, the weight gain in Group I was less than in Group II ($P<0.005$). The difference in body weights increased with time. (Text-fig 1).



TEXT-FIG 1. Effect of *T. cruzi* infection on body weight in weanling mice. On the Day 42 infected mice weighed more than control mice ($p < 0.05$). Afterwards the weight gain in control mice was significantly greater than in infected mice ($p < 0.005$).

Mortality. In Group I, life span ranged from 31 to 180 days, and 40% of the mice were dead within 84 days after inoculation.

Parasitemia. *T. cruzi* appeared in the blood on Day 12 after inoculation, reached an average peak of 28.3 trypanosomes/25 HPF on Day 34 and were no longer detected in 25 HPF of tail blood after 70 days. Parasitemia was present in all infected mice.

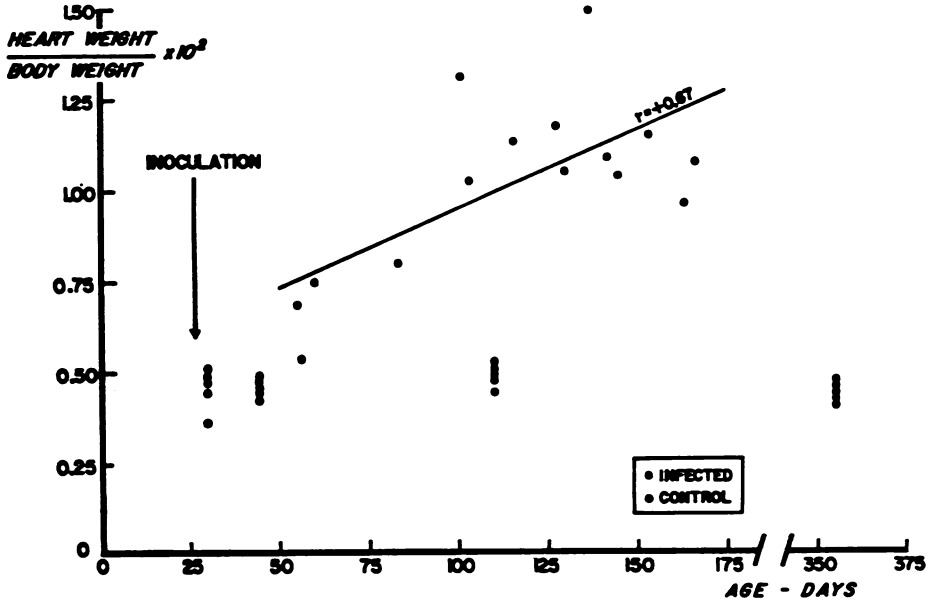
Heart Weight. Heart weight was expressed as heart weight/body weight $\times 10^3$ (HW/BW). In the control Group II, HW/BW was 0.455 under 50 days and 0.486 over 50 days, while in Group I it was 0.660 under 50 days and increased progressively to 0.704 between 50 and 84

Table 1. Heart Measurements, Organ Weights, and Number of Parasitic Aggregates per Section of Heart at Successive Time Intervals After Inoculation with *T. Cruzi* in Young C3H Mice (Group I) Compared to Control Animals (Group II)

			1a Under 50 days		1b 50–84 days		1c Over 84 days		Comparison	
		Groups	No.	Mean±SD	No.	Mean±SD	No.	Mean±SD	1a vs 1b vs 1c	p
Measurements										
Heart	Free wall	Infected	3	0.310±0.07	8	0.220±0.04	9	0.170±0.06	1a>1b	<0.05
Right ventricle	RVW (mm)	Control	4	0.252±0.035 (NS)	5	0.424±0.11 (0.001)	5	0.424±0.11 (0.001)	1a>1c	<0.01
	Cavity	Infected	3	0.833±0.144	7	1.30±0.49	8	2.65±1.07	1c>1b	<0.01
	RVC (mm)	Control	4	0.217±0.078 (0.001)	5	0.66±0.16 (0.02)	5	0.66±0.16 (0.001)	1c>1a	<0.02
Left ventricle	Free wall	Infected	3	1.15±0.15	8	1.14±0.19	7	1.3±0.21		NS*
	LVW (mm)	Control	4	1.10±0.12 (NS)	5	1.32±0.36 (NS)	5	1.32±0.36 (NS)		
	Cavity	Infected	3	0.75±0.42	8	0.75±0.37	6	0.65±0.33		NS
	LVC (mm)	Control		0.76±0.29 (NS)	5	0.73±0.56 (NS)	5	0.73±0.56 (NS)		
Thickness of septum		Infected	2	1.05±0.07	7	1.05±0.31	5	1.54±0.54		NS
		Control		1.315±.37 (NS)	5	1.22±0.23 (NS)	5	1.22±0.23 (NS)		
Ratios										
$\frac{\text{Heart weight}}{\text{Body weight}} \times 10^3$		Infected	3	0.660±0.108	7	0.704±0.195	10	1.09±0.21	1c>1a	<0.01
		Control	5	0.455±0.024 (0.02)	5	0.486±0.025 (0.05)	5	0.486±.025 (0.001)		
$\frac{\text{Liver weight}}{\text{Body weight}} \times 10^2$		Infected	1	7.21±0	8	6.46±1.34	8	8.04±1.45	1c>1a	<0.05
		Control	5	5.24±0.37 (0.02)	5	4.77±0.51 (0.02)	5	4.77±.51 (0.001)		
$\frac{\text{Spleen weight}}{\text{Body weight}} \times 10^3$		Infected	3	0.97±0.60	6	1.02±0.23	9	0.66±0.25	1b>1c	<0.02
		Control	5	0.447±0.037 (0.05)	5	0.272±0.052 (0.001)	5	0.272±.052 (0.01)		
Pseudocysts										
Pseudocysts Number/section of heart		Infected	3	22.2±25.5	8	2.18±1.36	9	2.3±1.67	1a>1b 1a>1c	<0.05 <0.05

* NS=Not Significant
Numbers in parentheses are p<.

days and 1.09 above 84 days after inoculation. HW/BW of the infected animals above 84 days was significantly greater than in animals below 50 days. HW/BW in infected animals exceeded significantly that of control animals at all stages. The regression of HW/BW ratios upon time for Groups I and II is presented in Text-fig 2. Heart weight in-



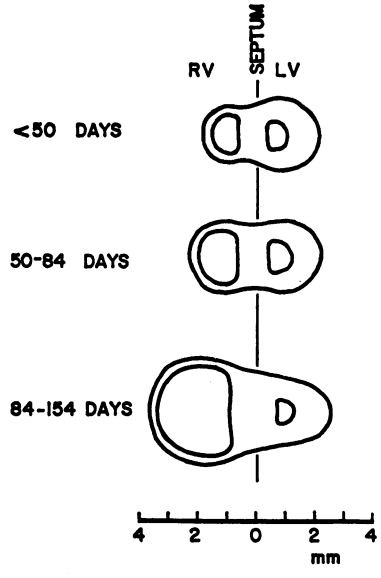
TEXT-FIG 2. Regression of $\frac{\text{Heart weight}}{\text{Body weight}} \times 10^2$ upon time in weanling infected (Group I) and control (Group II) mice. A significant increase in the HW/BW ratio with duration of myocarditis is seen. $Y = 0.633 + (0.00429 \times X)$; $r = +0.67$ ($P < 0.01$).

creased with the duration of myocarditis. In control animals, HW/BW ratio did not change before 110 days of age; from then on it decreased only slightly.

General Appearance and Pathology. Infected mice appeared thinner and less active than their controls. There was no edema or significant loss of hair. At necropsy, marked cardiomegaly was evident. Of the total circumference of the heart, 60–80% was occupied by the enlarged and dilated right ventricle and atrium (Fig 1). The left ventricle was never grossly enlarged. The liver was enlarged and markedly congested and had a typical "nutmeg" appearance in all infected mice. The lungs were congested. Four mice had bilateral serous pleural effusion. The spleen was enlarged and congested in all mice.

Measurements. Measurements are detailed in Table 1. The right

ventricular free-wall thickness (RVW) measured 0.310 mm in Group Ia, 0.220 mm in Ib and 0.170 mm in Ic. Thus, RVW decreased progressively and significantly with time. RVW in groups Ib and Ic measured less than in the control Group II. The diameter of the right ventricular cavity (RVC) measured 0.830 mm in group Ia, 1.30 mm in Ib and 2.65 mm in Ic. A progressive increase in RVC with time is noted. RVC in all stages was larger in infected than in control animals. A diagrammatic representation of right and left ventricular measurements in acute, subacute, and chronic myocarditis is shown in Text-fig 3. The right ventric-



TEXT-FIG 3. Diagrammatic representation of ventricular wall and cavity diameters of infected meanling mice (Group I) in acute, subacute, and chronic phases of myocarditis. Day 0 is the day of inoculation. *RV* = right ventricle; *LV* = left ventricle.

ular dilatation index (RVDI) was 38.5% in group Ia, 20% in Ib, and 7.3% in Ic. RVDI decreased significantly with time; the coefficient of correlation was -0.673 ($P<0.005$). In control Group II, RVDI was 83% under 50 days and 73.3% over 50 days, consistently greater than in the infected animals. In contrast, the left ventricular free wall and cavity measurements did not differ significantly between control and infected mice, or between subgroups of infected mice (Ia, Ib and Ic).

Liver and Spleen. Liver weight/body weight $\times 10^2$ increased by 47% in infected mice as compared to control animals. A tendency for increase in liver weight/body weight ratio was noted with time in the infected animals only. Significant splenomegaly was present in all infected animals; it tended to be maximal in the acute stage and decreased with time.

Microscopic Examination. All hearts examined from Group I had

diffuse involvement of the right ventricle and septum, and either diffuse or focal involvement of the left ventricle. In 11 mice (44%), however, the involvement of the left ventricle was primarily in the outer half with only sparse subendocardial cellular infiltration.

The myocardial lesions will be described in terms of acute, subacute, and late subacute and chronic myocarditis, according to the previously mentioned survival times.

Acute Myocarditis. The striking feature in mice surviving less than 50 days after inoculation was the extensive myocarditis with acute necrosis, in many areas associated with intramyofiber pseudocysts. These pseudocysts varied in size, contained parasites in the Leishmanial form and appeared to be surrounded by a thin membrane. The number of parasites in a packet varied with size but included 30 or more per fiber. As these pseudocysts grew larger, the myofiber underwent necrosis as revealed by granular and eosinophilic cytoplasm, loss of cross-striations, and intracellular edema, as well as nuclear degeneration. In some areas, rupture of the myofiber with exit of the parasites into the surrounding tissue (explosive lesion) was noted (Fig 2). After rupture, the fragmented myofiber disintegrated and eventually was replaced by granulation tissue.

The areas of acute inflammation consisted primarily of large collections of polymorphonuclear leukocytes with occasional lymphocytes and were scattered throughout the right ventricle and focally in the left ventricle. Many myofibers without evident intracellular parasites—even on serial sections—also underwent acute necrosis; such fibers were seen adjacent to pseudocysts but also at considerable distance from parasites. The interstitial tissue was severely edematous and contained focal collections of necrotic debris and polymorphonuclear leukocytes. During the acute phase of the disease, there were small foci of early granulation tissue consisting of mononuclear cell infiltration, small capillary sprouts and beginning collagen formation. Occasional necrotic myofibers were encrusted with calcium.

Subacute Myocarditis. Mice surviving from 50 to 84 days after inoculation showed, primarily, a subacute stage of myocarditis. Most hearts contained large areas of granulation tissue and early fibrosis which replaced the myofibers. The predominant inflammatory cells were histiocytes with some plasma cells and lymphocytes, intermingled with slender collagen fibers. Foci of acute myofiber necrosis were present. Some pseudocysts were still noted, although fewer in number than in the acute stage.

Late Subacute and Chronic Myocarditis. The cardiac lesions in late

surviving mice (84–154 days) were primarily subacute and chronic in nature. The chronic lesions in the left ventricle were composed of dense, small scars occupying areas of former complete muscle destruction. From these scars, thin bands of connective tissue infiltrated the surrounding tissue, enveloping viable muscle fibers and appearing, focally, to replace individual myofibers.

Myofibers which had resisted the parasites and infection, appeared normal. However, even at this stage some myofibers were undergoing acute necrosis. Occasional myofibers contained pseudocysts.

In some areas of subacute disease, there was extensive myocytolysis with replacement by mononuclear cells and capillary sprouts. Quite often, acute, subacute and chronic lesions were adjacent to one another and separated only by a few normal-appearing myofibers.

The right ventricle in long-surviving mice was replaced, almost entirely, by dense fibrous tissue containing a few chronic inflammatory cells and only a few normal myofibers in the thickness of its wall (Fig 3 and 4). This finding accounted for the extreme thinness of the markedly dilated right ventricular wall.

GRADING. The degree of fibrosis present in the subacute and chronic stages of myocarditis tended to agree with the degree of myocarditis. Thus 10 of the 20 weanling mice had severe myocarditis graded 2–3+ or 3+, and the fibrosis was also grade 3+. The other 10 mice had less extensive myocarditis (1–2 +), and the fibrosis was similarly less.

CARDIAC GANGLIA. In the atrial wall, cardiac ganglia were seen in 15 of the 20 hearts examined from Group I, and all showed degenerative changes. The most common lesion, in the acute phase of the disease, was marked edema of the ganglion with vacuolization of individual cells. Some nuclei were undergoing karyorrhexis and pyknosis. Rarely, pseudocysts were present in the ganglia (Fig 5 and 6). In other hearts, cellular infiltrates, primarily lymphocytic, were noted both within the ganglia and in the perineural space. Dilated lymphatic channels were also noted.

In long-surviving animals (over 84 days) there was fibrous replacement of ganglia by slender strands of connective tissue arising from the periganglionic tissue and extending into the center. These fibrous strands encircled individual ganglion cells, some of which were edematous and necrotic (Fig 7).

Five of the mice had no visible ganglia in the sections, but in 2 of these, cardiac autonomic nerves showed marked perineural edema and focal chronic inflammatory infiltration.

MURAL THROMBI. Antemortem mural thrombi were present in 11 of

the 20 mice in Group I. These were located in the right atrium in 3 animals, in the right ventricle in 5, and in both cavities in 3. The thrombi were in all stages of organization, and most were firmly adherent to the underlying endocardium (Fig 4). Many thrombi completely filled the chamber in which they were found. Others were smaller and already re-endothelialized. Several of the oldest mice in this group showed evidence of mural thrombi, replaced completely by fibrous tissue, which on gross examination appeared as whitish nodules on the endocardial surface.

OTHER OBSERVATIONS. All mice showed evidence of skeletal myositis, varying in degree, primarily consisting of loss of muscle fibers and replacement by sheets of subacute and chronic inflammatory cells and by fibrosis. In 3 mice, parasites were seen in muscle fibers. With time, acute inflammatory cells tended to decrease and fibrosis tended to increase.

Chronic passive congestion of the liver was evident in all mice, with superimposed acute hyperemia in some. Hyperplasia of the white pulp of the spleen was evident in 50% of the mice, and chronic passive congestion in most. There was evidence of chronic passive congestion of the lungs in 15 of the 20 mice. In addition, 6 mice had foci of interstitial pneumonitis.

Adult Mice (Groups III and IV; Table 2)

Qualitatively, the results resembled those observed in the weanling animals. Quantitatively, in the acute phase of myocarditis, the mortality was less in the adult Group III than in the weanling Group I.

In the infected mice, mean survival time was significantly decreased. As in the weanling mice, diameters of the left ventricular free wall and cavity did not differ from the control mice. The predominent change was marked right ventricular dilatation (Fig 8 and 9). In the chronic phase of the infection, measurements of right ventricular wall and cavity in young mice (Group Ic—above 84 days) resembled closely those observed in adult mice (Table 2, Group III). Sixty per cent of the adult, infected animals survived 160 days after inoculation. Ventricular measurements under 100 days, at 100–160 days, and above 160 days did not differ significantly. All mice which succumbed in the subacute or chronic phase of myocarditis developed right ventricular cavity diameters of about 2.40 mm, and their right ventricular free wall measured 0.16 mm, irrespective of their age at the time of inoculation.

Microscopic Pathology in Older Mice. Seventeen animals from Group III were examined microscopically, having survived from 58 to

Table 2. Salient Measurements in Adult C3H Mice Infected with *T. Cruzi* (Group III) Compared to Control Animals (Group IV)

	Infection Mice Group III			Control Mice Group IV			
	N	Mean	SD	N	Mean	SD	P
Mean survival days	24	155.0	46.9	24	>300	—	<0.001
Peak Parasitemia							
T. cruzi/25 HPF	23	27.8	10.3	—	—	—	—
Right Ventricle							
Free Wall RVW mm	14	0.163	0.016	5	0.500	0.106	<0.001
Cavity RVC mm	14	2.463	0.263	5	0.496	0.173	<0.001
Left Ventricle							
Free Wall LVW mm	14	1.316	0.146	5	1.200	0.165	NS
Cavity LVC mm	14	0.947	0.517	5	1.260	0.163	NS
$\frac{\text{Heart Weight}}{\text{Body Weight}} \times 10^3$	18	0.669	0.089	21	0.420	0.024	<0.001
$\frac{\text{Liver Weight}}{\text{Body Weight}} \times 10^3$	17	6.186	1.209	21	4.921	.366	<0.001
$\frac{\text{Spleen Weight}}{\text{Body Weight}} \times 10^3$	16	0.687	0.176	21	0.275	.044	<0.001

218 days after inoculation. Mortality in the acute phase was much less than in Group I. Thus only 2 died at 58 days and 1 at 93 days; the remainder survived from 133 days to 218 days.

The 2 mice which died on Day 58 showed minimal myocarditis, primarily acute with some subacute changes, similar to those described above. No thrombi were present. The mouse which died on Day 93 had diffuse myocarditis as well as fibrosis. There were areas of chronic myocarditis, and thrombi were present in the right atrium.

All other mice showed moderate to marked diffuse myocarditis (2–3+) with comparable degrees of fibrosis. In the oldest mice the prominent feature was fibrosis with slight infiltration by lymphocytes and some plasma cells. However, all hearts, irrespective of age, had some foci of acute necrosis as well as intracellular parasites. Eleven of the 13 mice over 133 days old had mural right ventricular and/or atrial thrombi. All three ganglia examined showed varying degrees of degeneration, including vacuolization, edema, nuclear pyknosis and fibrosis.

The pathologic findings closely resembled those described in the infected young mice, except that more chronic stages were studied. This late chronic disease was almost indistinguishable from that seen in group Ic.

Discussion

A Colombian strain of *T. cruzi*, which in earlier passages in mice had

been characterized as relatively mild,[2,4] produced congestive heart failure in most animals, as manifested by marked cardiomegaly, hepatomegaly, hepatic and pulmonary congestion after the hundredth passage. Right ventricular failure dominated over pulmonary congestion. Consistently, the right ventricle was markedly dilated, and the myocarditis was more evident in the right ventricular than in the left ventricular wall. Furthermore, intracardiac thrombi, seen in 55% of young and 69% of adult animals, were limited to the right side. Cardiac ganglia were consistently involved by the disease. Thus, for the first time to our knowledge, the full-blown, severe form of chagasic cardiomyopathy, as clinically known in man [8,9] and comprising congestive heart failure, intracardiac thrombosis, and degeneration of cardiac ganglia, has been reproduced consistently in a laboratory animal. In earlier passages of the same parasite, disease of comparable severity was seen only in occasional animals in association with forced exercise,[3] dietary ethanol,[5] or immunosuppression.[6]

The studies made possible by the availability of the present model of severe, decompensated Chagas' disease yielded some insight into the pathogenesis of the syndrome. The fact that the increase in severity of the lesions and appearance of congestive heart failure occurred with a change in virulence of the parasite [3] in the same inbred strain of mice constitutes an argument for the central role of the parasite in the pathogenesis of the lesion, and against immune and autoimmune mechanisms as the major influence.[10,11] The ease of demonstration of the parasite in the myocardium, dominance of infiltrative and degenerative lesions, as well as the rarity of perivascular lesions in the present material are in agreement with this view. Ischemia, secondary to compromise of the capillary circulation by the acute inflammatory reaction and the later contracting scars, may also contribute to the pathogenesis of the myocarditis.

The dominance of right ventricular involvement in the experimental model has been striking. Comparable pathologic analyses of relative involvement of the two ventricles in the human form of the disease are not available. When, however, acute Chagas' disease is associated with clinical evidence of heart disease, the picture tends to be one of cardiomegaly and predominant right heart failure, with hepatic congestion and edema.[8,12] In the chronic phase of the human disease, involvement of the right ventricle has been suggested by the dominance of right bundle branch block on the electrocardiogram.[8,13] Köberle [9] pointed out that hypertrophy and dilatation are seen more prominently in the

right-sided chambers of the heart. Köeberle [9] and, more recently, Suarez [14] found thromboses more frequently in the right heart.

How can this predilection of chagasic cardiomyopathy for the right side of the heart be explained? Although after intraperitoneal inoculation the parasites may pass first through the right heart, there is no evidence that more parasites reach the right than the left ventricular muscle, nor that the conditions for growth and multiplication are better in the right heart. If pulmonary hypertension were a feature of Chagas' disease, the added right ventricular pressure load might account for predominance of right ventricular dilatation and failure. In one clinical case of chronic disease in which pulmonary arterial pressure was measured, there was only mild pulmonary hypertension.[15] Preliminary measurements of right ventricular pressures in mice with the experimental disease in this laboratory have shown no evidence of significant pulmonary hypertension.[16]

We consider the following sequence the most likely explanation of the data. Initial diffuse involvement of cardiac muscle leads to biventricular enlargement and failure. Whereas left ventricular systolic pressure is likely to remain normal or actually fall, right ventricular systolic pressure is likely to increase, at least slightly. Right ventricular dilatation will result in thinning of the wall and a reduction of the volume-elasticity coefficient. According to the rule of Laplace, increase in the radius of a spherical chamber enhances the increase in wall tension for a given pressure.[17] This may lead to progressive dilatation and further weakening of the right ventricle. At the same time, right ventricular failure presumably reduces left ventricular filling and cardiac output, and thus may spare the left ventricle. Hemodynamic studies in animals with the experimental disease, now in progress, will test this hypothesis.

Whatever the factors responsible for dominance of right ventricular lesions and failure in acute and subacute chagasic myocarditis, they may not be limited to this form of diffuse cardiomyopathy. Dominance of right ventricular involvement and failure has been described in endomyocardial fibrosis [18] and in certain high output states like beriberi.[19,20] Right ventricular failure also tends to be clinically dominant in acute viral or idiopathic myocarditis and in acute rheumatic fever, especially in children.[21]

It is hoped that the model of congestive heart failure described in this communication may serve further to elucidate the pathophysiology not only of chagasic cardiomyopathy, but also of diffuse cardiomyopathy with intracardiac mural thrombi and congestive heart failure in general.

Summary

Infection with *Trypanosoma cruzi* (Colombian) in 30 weanling and

24 adult C3H mice has been shown to produce extensive myocarditis. The cardiac syndrome is characterized predominantly by right ventricular failure, manifested in marked dilatation of the right ventricular cavity and decrease in thickness of the right ventricular free wall, and by increase in heart weight/body weight and liver weight/body weight ratios. Mural thrombi were found in the right atrium and/or ventricle in 55% of infected weanling and in 69% of adult mice. The left ventricular measurements did not differ from controls. Consistent involvement of cardiac ganglia was demonstrated. The pathogenesis of chagasic cardiomyopathy and the preferential involvement of the right ventricle are discussed in light of the data. Further use of this experimental preparation as a model of congestive heart failure of natural cause is suggested.

References

1. KLINE, I. K., KUMAR, R., and ABELMANN, W. H. Right ventricular involvement in experimental Chagas' myocarditis. (Abst) *Amer J Clin Path 50*: 599, 1968.
2. FEDERICI, E. E., ABELMANN, W. H., and NEVA, F. A. Chronic and progressive myocarditis and myositis in C3H mice infected with *Trypanosoma cruzi*. *Amer J Trop Med 13*:272–280, 1964.
3. MILLER, H., and ABELMANN, W. H. Acute experimental myocarditis due to *Trypanosoma cruzi*. Exercise-induced cardiac hypertrophy. *Arch Path 84*: 627–632, 1967.
4. ELSON, S. H., and ABELMANN, W. H. Effects of muscular activity upon the acute myocarditis of C3H mice infected with *Trypanosoma cruzi*. *Amer Heart J* 69:629–636, 1965.
5. MILLER, H., and ABELMANN, W. H. Effects of dietary ethanol upon experimental Trypanosomal (*T. cruzi*) myocarditis. *Proc Soc Exp Biol Med 126*:193–198, 1967.
6. KUMAR, R., KLINE, I. K., and ABELMANN, W. H. Effects of immuno-suppression on experimental myocarditis (Chagas' Disease). *Circulation (Suppl IV) 38*:120, 1968.
7. BEZNAK, M. Behavior of weight of heart and the blood pressure of albino rats under different conditions. *J Physiol 124*:44–63, 1954.
8. LARANJA, F. S., DIAS, E., NOBREGA, G., and MIRANDA, A. Chagas' Disease. A clinical, epidemiologic and pathologic study. *Circulation 14*:1035–1060, 1956.
9. KÖBERLE, F. Die Chronische Chagaskardiopathie. *Virchow Arch Path Anat 330*:267–295, 1957.
10. PIZZI, T., RUBIO, M., and KNIERIM, F. Immunologia de la enfermedad de Chagas. *Bol Chile Pazasit 9*:35, 1956.
11. KOZMA, C., JAFFE, R., JAFFE, W. Estudo experimental sobre a patogenia das miocardites. *Arq Brazil Cardio 13*:155–161, 1960.
12. NETO, V. A. Contribuicao ao conheumento da forma aguda da doenca de Chagas. Tese apresentada à Faculdade de Medicina da Universidade de Sao Paulo. Sao Paulo, 1958.
13. ROSENBAUM, M. B., and ALVAREZ, A. J. Electrocardiogram in chronic chagasic myocarditis. *Amer Heart J 50*:492–527, 1955.

14. SUAREZ, J. A. Coronariografia post mortem en miocardiopatia Chagasica. *Gac Med Caracas* 75:57–93, 1967.

15. MASSUMI, R. A., and GOOCH, A. Chagas' myocarditis. *Arch Intern Med 116*: 531–536, 1965.

16. KUMAR, R., WAGNER, R., and ABELMANN, W. H. Unpublished data, 1968.

17. WOLF, A. V. Demonstration concerning pressure-tension relations in various organs. *Science 115*:243–244, 1952.

18. ABRAHAMS, D. G. Endomyocardial fibrosis of right ventricle. *Quart J Med* 55:1–20, 1962.

19. BLACKET, R. B., and PALMER, A. J. Hemodynamic studies in high output beri-beri. *Brit Heart J 22*:483–501, 1960.

20. WENCKEBACH, K. F. Heart and circulation in a tropical avitaminosis (Beri Beri). *Lancet* 2:265–268, 1928.

21. BLAND, E. F., and JONES, T. D. Rheumatic fever and rheumatic heart disease; 20 year report on 1000 patients followed since childhood. *Circulation* 4:836–843, 1951.

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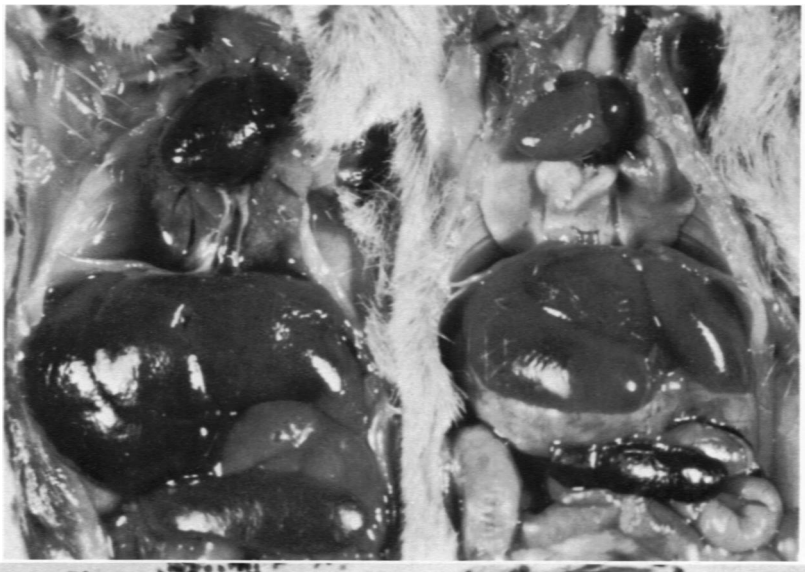


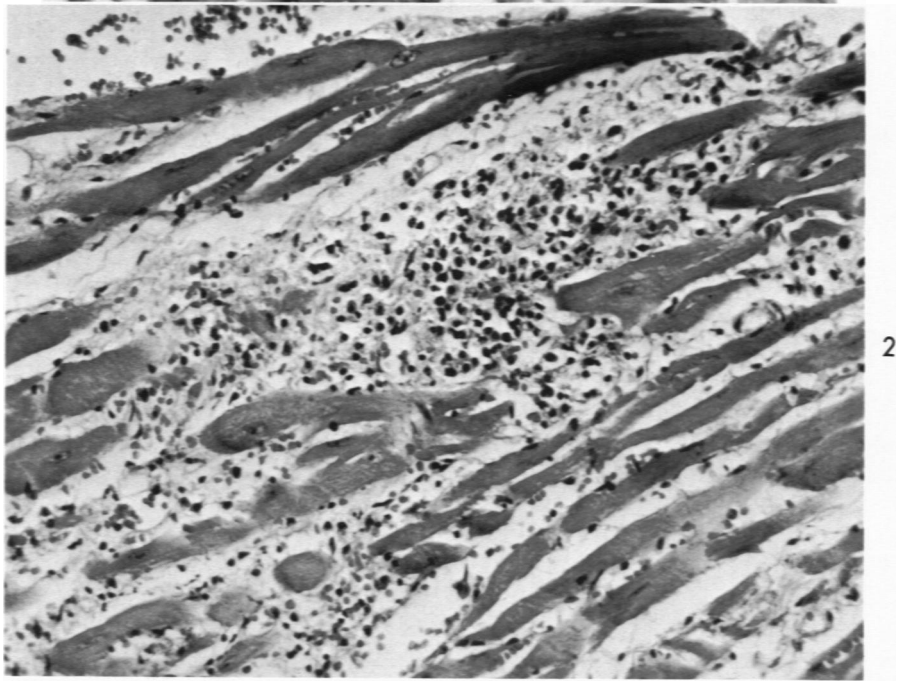


Fig 1. Organs in situ of 42-week-old mouse, 24 weeks after infection from Group III, weighing 19.5 g with heart weight 135.2 mg (*left*), and age-matched control mouse weighing 29.3 g, with heart weighing 95 mg (*right*). Marked cardiomegaly, predominantly of right-side chambers, is seen in infected animal. Note also enlarged, congested liver and spleen.

Fig 2. "Explosive lesion" in right ventricle of weanling mouse (Group I) 104 days after inoculation showing disintegration of myofibers with marked inflammatory cell reaction. H & E. × 270.

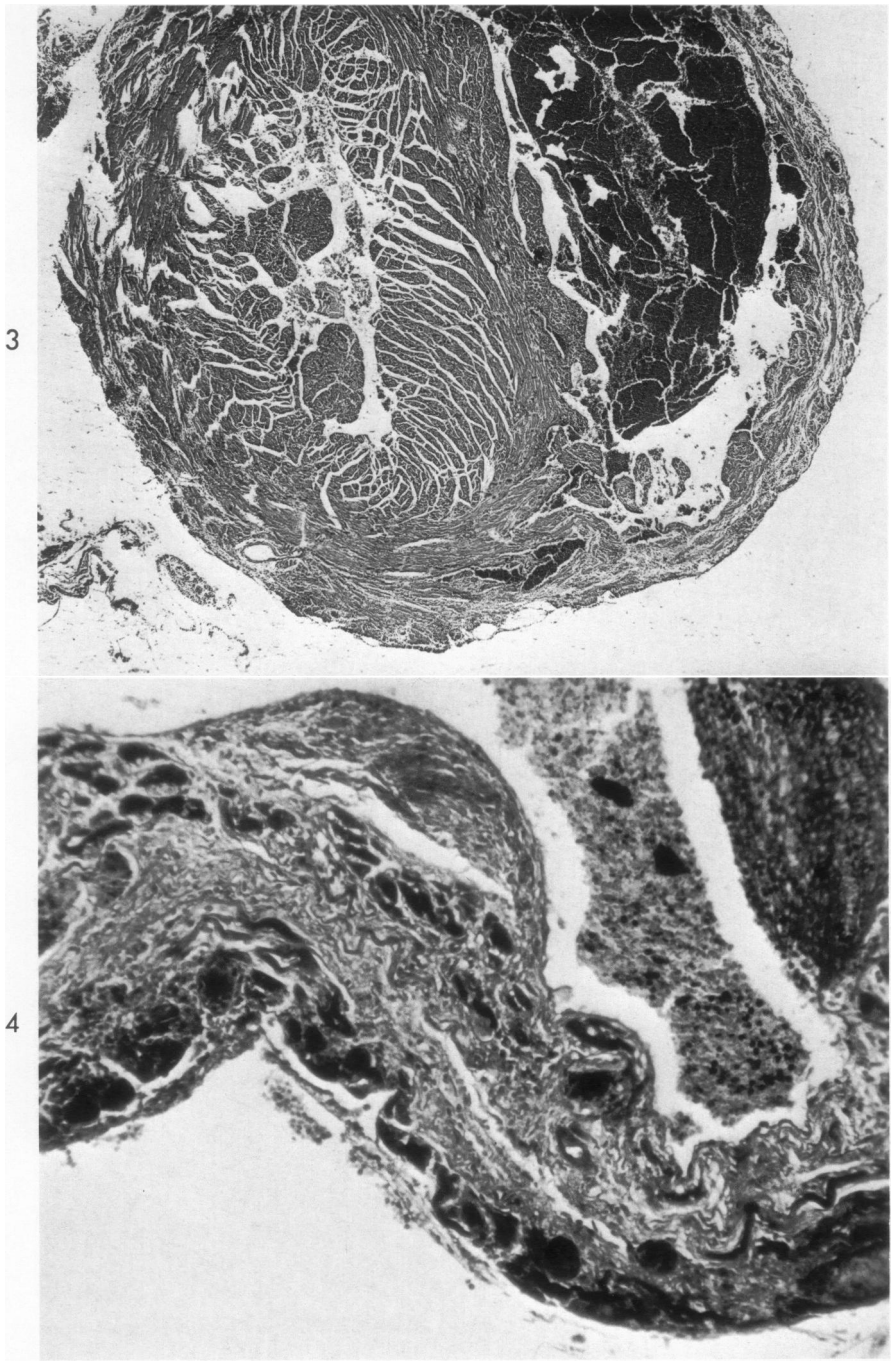


Fig 3. Severe myocarditis in mouse from Group I, 77 days after inoculation, showing marked changes in right ventricle (*right*) with only sparse reaction in left ventricle (*left*). H & E. × 23.

Fig 4. Mouse from Group I, 154 days after inoculation, showing thinned right ventricular free wall with virtually complete replacement by fibrous tissue (light-staining). Remaining viable myofibers are dark-staining. An organized mural thrombus is present at left and recent thrombus at upper right. Combined Masson and elastic tissue stain. × 190.

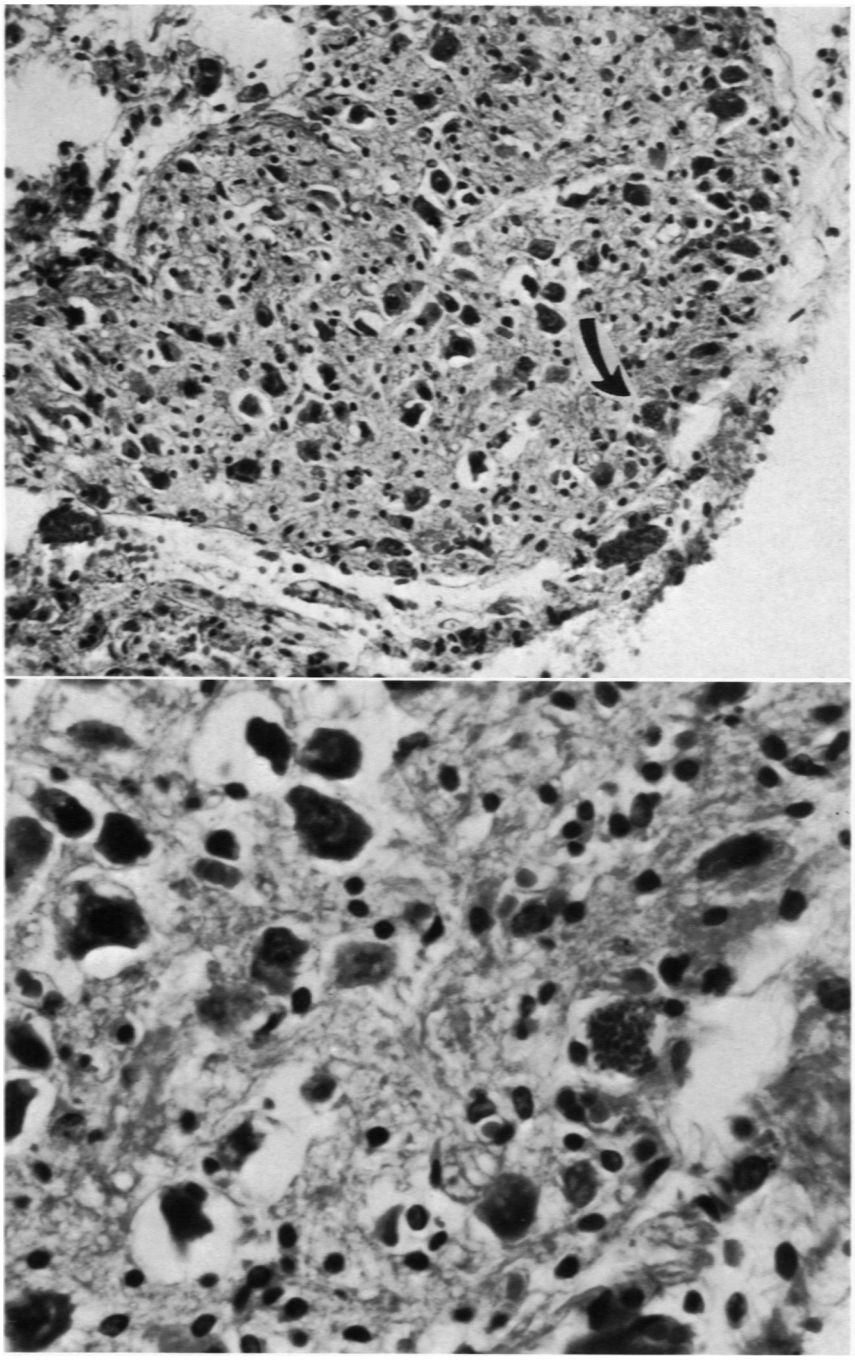
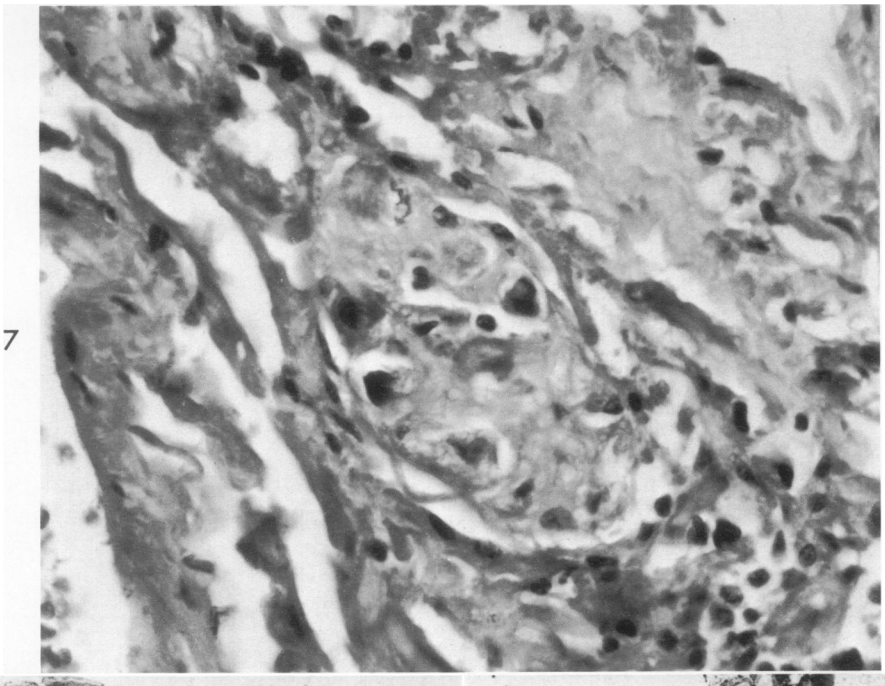


Fig 5. Cardiac ganglion from infected mouse of Group I, 29 days after inoculation, revealing chronic inflammatory cell infiltration, ganglion cell degeneration, edema, and pseudocyst in one ganglion cell (*arrow*) H & E. × 270.

Fig 6. Higher magnification of Fig 5 showing same changes and pseudocyst with leishmanial forms of *T. cruzi* in ganglion cell. H & E. × 700.



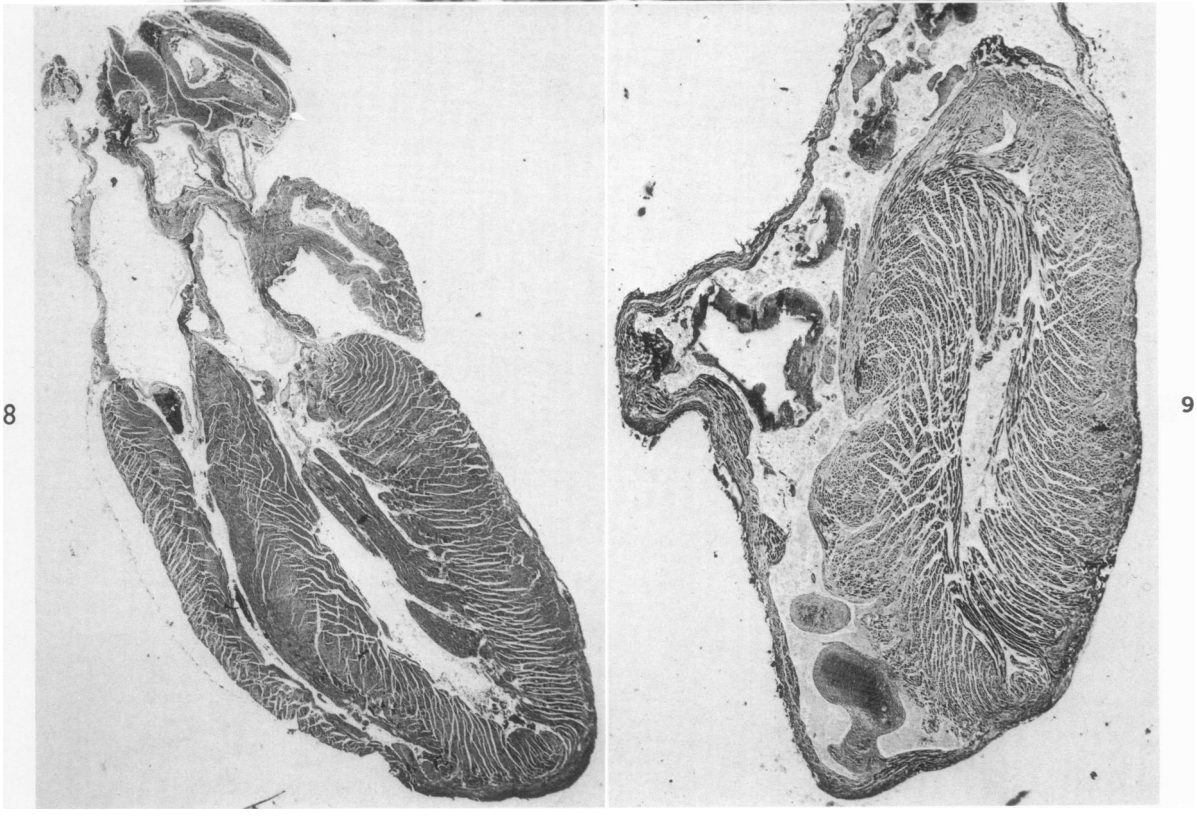


Fig 7. Cardiac ganglion from Group I mouse, 84 days after inoculation, showing extension of fibrous tissue into ganglion from periphery. Only a few gaglion cells remain. H & E. × 600.

Fig 8. Coronal section of heart from 130-day-old control mouse of Group II showing normal size of right and left ventricles. H & E. × 15.

Fig 9. Coronal cardiac section of adult mouse of Group III with Chagas' myocarditis, 156 days after inoculation, showing marked right ventricular thinning and dilatation. Note presence of mural and intracavitary thrombi and relative uninvolvement of left ventricle (Compare with Fig 8). H & E. × 15.