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12 – Francisco S. Laranja, Emmanuel Dias, Genard Nóbrega & Aloisio Miranda - Chagas' disease: a clinical, epidemiologic, and pathologic study.

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Chagas' disease: a clinical, epidemiologic, and pathologic study.
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Francisco da Silva Laranja Filho (1916-1989)

Médico nascido no Rio Grande do Sul, foi diretor do Instituto Oswaldo Cruz e pesquisador do Centro de Estudos e Profilaxia da Moléstia de Chagas de Bambuí, dedicando-se especialmente às pesquisas em cardiopatia chagásica.

Emmanuel Dias (1908-1962)

Médico nascido no Rio Janeiro, foi diretor do Centro de Estudos e Profilaxia da Moléstia de Chagas de Bambuí e destacou-se pela realização de importantes investigações científicas sobre a tripanossomíase americana e pelas primeiras ações de controle da doença.

Genard da Cunha Nóbrega (1872-1948)

Médico paraibano do Instituto Oswaldo Cruz, desenvolveu trabalhos sobre clínica e terapêutica da doença de Chagas. Com Laranja, Dias e Miranda, empreendeu uma revisão da forma crônica da moléstia com ênfase na cardiopatia chagásica.

Aloisio Miranda (s.d.)

Com Laranja, Dias e Nóbrega, empreendeu uma revisão clássica da forma crônica da doença de Chagas, enfocando especialmente a cardiopatia chagásica.

Chagas' Disease

A Clinical, Epidemiologic, and Pathologic Study

By F. S. LARANJA, M.D., E. DIAS, M.D., G. NOBREGA, M.D., AND A. MIRANDA, M.D.

A study of the most important clinical and pathologic aspects of Chagas' disease has been presented, on the basis of the analysis of 180 cases of acute infection (11 with autopsy), 657 cases of chronic asymptomatic infection, and 683 cases of chronic Chagas' heart disease (21 autopsied cases with *Schizotrypanum cruzi* in myocardium).

CONSIDERABLE advances in the clinical aspects of Chagas' disease have been made in the last decade. In the historical review of our knowledge 3 periods may be recognized.¹⁵ 1. The first period began with the clinical descriptions made by Chagas.^{2, 3} He described an acute form⁴ and several chronic forms^{3, 5} of American trypanosomiasis. He was greatly impressed^{6, 7} by the cardiac disturbances exhibited by many persons from the region in which the disease was discovered and claimed that such cardiac disturbances were related to chronic American trypanosomiasis.

2. From 1913 to 1943 acute cases of Chagas' disease were described in 15 American countries. Various authorities doubted an etiologic relationship between *Schizotrypanum cruzi* (*Trypanosoma cruzi*) infection and the chronic forms described by Chagas; only a few cases of chronic Chagas' disease were reported up to 1945. The concept of Chagas' disease as an uncommon acute disease was generally accepted. The true medical and social importance of this endemic infection was not appreciated.

3. Carlos Chagas' original observations on the cardiac disturbances in chronic *S. cruzi* infection have been confirmed and considerably extended¹⁰⁻¹⁸ in the last 10 years. Epidemiologic studies, observations of the clinical manifestations, the description of the electrocardiographic changes, improved laboratory diagnosis, the pathologic studies, and, finally, the production of a chronic type of heart

disease similar to the human in dogs experimentally infected with *S. cruzi*—all these studies have provided a firm basis for defining chronic Chagas' heart disease as a distinct clinicoanatomic entity.¹⁷

Observations have shown the common occurrence in some Brazilian districts of both cardiospasm (megaesophagus) and chronic trypanosomiasis. Patients from such areas with cardiospasm show a particularly high percentage (up to 97 per cent) of positive complement-fixation tests for Chagas' disease and electrocardiographic changes similar to those usually found in chronic Chagas' heart disease.^{13, 23} These facts suggest a possible etiologic relationship between Chagas' disease and cardiospasm in those areas. The subject requires further investigation.

ETIOLOGY

S. cruzi has a typical trypanosome blood form, characterized by a large, terminal or subterminal blepharoplast. In the tissues the flagellates undergo regressive changes resulting in the formation of leishmaniform organisms that divide by binary fission, thus forming intracellular colonies of parasites. The myocardial fibers seem to be the most important site of multiplication of *S. cruzi*.

In sections from the myocardium the parasite usually assumes the morphology of leishmania bodies (fig. 1a), which are round corpuscles measuring 4 by 2 or 3 by 1.5 microns, containing an ovoid nucleus and a rodlike blepharoplast. The fibers occasionally contain flagellate or preflagellate forms (fig. 1b) of *S. cruzi*; in this case the morphology of individual microorganisms usually is not clearly seen in

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FIG. 1. Leishmanial forms (a) and preflagellate forms (b) of *S. cruzi* in the myocardial fibers. Dog, no. 35. Experimental infection. Death on the thirty-sixth day of disease, with pronounced cardiac dilatation, right bundle-branch block, atrial fibrillation, and congestive heart failure.

tissue sections. Care should be taken in distinguishing such forms from other intracellular parasites, especially *Toxoplasma*.

S. cruzi is virulent to man and several animals and is easily cultivated in vitro. Its virulence is variable, depending on the source of the strain and on other factors. The blood trypanosome form is picked up by the insect vector.

EPIDEMIOLOGY, GEOGRAPHIC DISTRIBUTION, AND INCIDENCE

The insect vectors of *S. cruzi* are Hemiptera belonging to the family Reduviidae, subfamily Triatominae. The most important species belong to the genera *Triatoma*, *Panstrongylus*, and *Rhodnius*. More than 30 species of triatomid bugs have been found infected with *S. cruzi*.⁸ *Triatoma infestans*, *Panstrongylus megistus*, and *Rhodnius prolixus* are the principal vectors of Chagas' disease in large areas of South and Central America.

Infected triatomid bugs are widely distributed in this continent, from the United

FIG. 2. Areas in which triatomid bugs infected with *S. cruzi* have been found. Data collected from the literature up to 1954.

States to Argentina (fig. 2). *S. cruzi* has never been detected in triatomines outside the American continent, although it was found in monkeys in Java (Malamos).

Triatominae are strictly hematophagous insects and they get their flagellates from the blood of vertebrate hosts; so, the presence of infected bugs depends upon the existence of infected vertebrates. To the species well adapted to human dwellings, such as *T. infestans*, *P. megistus*, and *R. prolixus*, man and domestic animals are the main sources of infection.

In rural and semirural areas of the Latin American countries there are huge regions infested with domestic triatomid bugs. The primitive mud huts covered with thatched roofs are favorable habitats for such species. The vectors live in hiding places, in holes and cracks in the walls, in beds, behind trunks, pictures, etc. In the United States there are

several species infected with *S. cruzi*, but they seldom breed in homes, although these are frequently invaded by flying insects during the summertime.

The triatomid bugs harbor *S. cruzi* in their digestive tract and apparently they suffer no harm as a result of being infected with the flagellate. Cyclical development of the parasite takes place in the stomach, duodenum, and rectum of the bugs. The blood trypanosome forms pass through the crithidial (multiplication) stage, and give rise to the metacyclical (infective) forms, which are eliminated with the excreta of the insects. Normally, transmission of the disease is effected through contamination of mucosa or skin with infected dejections eliminated by the bugs during or soon after feeding. Transmission of Chagas' disease to man by blood transfusion, or via placenta, or accidentally by inoculation of blood from infected animals, may occur.

Human infection with *S. cruzi* has been detected so far in all countries over a region extending from the United States (Texas) to Argentina, with the exception of Honduras and British and Dutch Guianas. In the last 10 years a large number of cases of chronic Chagas' heart disease has been diagnosed, particularly in Brazil and Argentina. In some areas of the Brazilian States of Minas Gerais, São Paulo, and Bahia, *S. cruzi* infection is evidently one of the most common etiologic factors of chronic heart disease. Nevertheless, the geographic distribution and incidence of human infection with *S. cruzi* as well as the incidence and severity of chronic Chagas' heart disease in different endemic areas are incompletely known. In most of the huge rural and semirural areas in which infected triatomid bugs have been found, no adequate diagnostic surveys for human cases of Chagas' disease have yet been carried out. There is still a great deal of work to be done, before we shall be able to appreciate the significance of Chagas' disease to the countries of the American Continent.

ACUTE CHAGAS' DISEASE

Acute infection may occur at any age, but usually occurs in the first years of life (fig. 3).

FIG. 3. Age and sex distribution of 171 cases of acute Chagas' disease.

Acute cases are more frequent in the summer months. The clinical picture may be quite easily recognized in endemic areas. The acute period is manifested by general malaise, fever, abundant sweating, muscular pains, irritation, anorexia, and sometimes vomiting and diarrhea; local signs of portal of entry of the parasite in the organism, lymph node enlargement, generalized edema, and in some cases anasarca; hepatomegaly and moderate splenomegaly, and occasionally cutaneous eruptions (schizotrypanides); symptoms and signs of heart involvement, and in some cases (usually fatal) symptoms and signs of central nervous system involvement (acute meningoencephalitis). Laboratory findings include leukocytosis with pronounced lymphocytosis, increased blood sedimentation rate, widening of the coagulation band on Weltman's reaction, decrease in serum albumin fraction, and frequently increase of certain globulin fractions of blood sera during the edematous period, as well as abnormalities of some other liver function tests.

Cardiac Involvement

Cardiac involvement of greater or lesser intensity probably occurs in almost every case of acute Chagas' disease, but is frequently not recognized. A review of the 19 cases of acute Chagas' disease so far reported with post-

TABLE 1.—Clinicopathologic Findings in Eleven Cases of Acute Chagas' Disease

Case, reg. no.	Age and sex	Duration of disease (approx.)	Death	X-ray of chest	Electrocardiogram	Chief anatomic findings:*	
						Heart	Other organs
1 429 J.S.	2 mos. M	10 days	Broncho-pneumonia, pyothorax	Normal cardiac area	Rate: 180; AQRS: approx. +95° AT +35° QT 0.20"	Acute, moderately intense (++) myocarditis, preponderant in subepicardial areas left ventricle; slight degenerative changes of myocardial fibers; edema intima and media of small arteries of right ventricle; numerous myocardial fibers parasitized with <i>S. cruzi</i>	Bronchopneumonia and fibrinopurulent pleuritis at right side, right pyothorax; fatty degeneration liver
2 519 C.M.S.	5 mos. F	2 mos.	Cardiac failure	—	(Made 7 days before death) Rate: 170 P-R: 0.12" AQRS: +80° AT +5°	Acute, severe (+++++) myocarditis, preponderantly subendocardial and more severe at ventricles; slight degenerative changes of myocardial fibers; <i>S. cruzi</i> within myocardial fibers	Passive congestion lungs, liver, and kidneys
3 589 D.S.	7 yrs. F	2 mos.	Cardiac failure, convulsions	—	—	Acute, diffuse myocarditis of slight (+) intensity with disseminated degenerative changes of myocardial fibers; slight degree of fibrosis of left ventricle; <i>S. cruzi</i> within myocardial fibers	Passive congestion lungs, liver, and kidneys; fat degeneration of liver
4 588 F.D.	2 yrs. F	3½ mos.	Cachexia	Moderate enlargement of cardiac shadow (pericardial fluid) until 2 weeks before death	Abnormal: Rate: 150. PR 0.16". Low voltage of QRS in extremity leads. Prolonged Q-T interval. Subendocardial injury pattern	Acute, diffuse, moderately intense (++) myocarditis with slight degenerative changes of myocardial fibers; slight degree of fibrosis of left ventricle; <i>S. cruzi</i> within myocardial fibers	Fat degeneration liver and kidneys
5 408 G.M.S.	5 yrs. F	22 days	Convulsions, congestive heart failure	—	Abnormal: Rate: 130. Prolongation of P-R interval. Complete RBBB. Pattern of subendocardial injury, followed by subepicardial injury of anterior wall	Acute, very severe (+++++) diffuse myocarditis, predominantly subendocardial and on the basal portion of the ventricles; severe, disseminated, hyaline degeneration of myocardial fibers; Heavy parasitism of myocardial fibers by <i>S. cruzi</i> ; Extensive lesions involving all the portions of the His-Tawara system, and apparently more severe in initial portion of right bundle of His	Chagasic encephalitis; tuberculous bronchial and hilar lymph nodes; serous hepatitis; anasarca (bilateral hydrothorax, hydropneumothorax, and hydropneumoperitoneum); passive congestion of lungs, spleen, kidneys, and adrenal glands

6 252 A.S.	2 yrs. M	3 mos.	Convulsions	Normal cardiac area (27 days before death)	Abnormal: Rate: 136. QRS 0.07" AQRS ap- prox. +135° AT ap- prox. +90°. T wave neg. in V ₁ , pos. in V ₂ and diphaseic - + in V ₅ , V ₆ .	Acute, severe (+ + +) diffuse myocardi- tis, with moderately severe degenera- tive changes of myocardial fibers and interstitial fibrosis; lesions were more severe in ventricles, particularly left; circumscribed pericarditis; <i>S. cruzi</i> in myocardial fibers	Passive congestion lungs, liver, kidneys, and spleen
7 295 J.B.	4 yrs. M	6 mos.	Congestive heart fail- ure	—	Abnormal: Rate: 185. Prolongation of P-R interval. Low voltage of QRS and T waves. AQRS +110°. AT +10°.	Acute, diffuse myocarditis of slight (+) intensity, with slight degree of de- generative changes of myocardial fibers and conspicuous interstitial fibrosis of myocardium; circumscribed acute pericarditis; area of fibrous thickening of endocardium at base of left ventricle; <i>S. cruzi</i> in myocardium	Edema and hyperemia of lungs; bronchopneu- monia; pulmonary infar- ction; fat degeneration of liver
8 270 J.C.	2 yrs. M	6 mos.	Congestive heart fail- ure	—	Abnormal: Rate: 140. Low voltage QRS ex- tremity and precor- dial leads. AQRS +90°. Low T waves in standard leads, neg. in V ₁ , V ₂ , V ₃ , diphaseic - + in V ₄ , isoelectric in V ₅	Acute, severe (+ + +), diffuse and focal myocarditis with slight degree of de- generative changes of myocardial fibers; moderate interstitial fibrosis; various myocardial fibers, particularly in left ventricle, parasitized with <i>S.</i> <i>cruzi</i> ; conspicuous reduction of lumen of anterior descending coronary artery by atheromatous (?) plaque	Passive congestion of lungs, liver, spleen, and kidneys
9 1650 E.L.E.	10 mos. M	20 days	Convulsions	—	Abnormal: Rate: 150. Low voltage of P waves and QRS com- plex in extremity leads. QRS 0.06". AQRS approx. -170°. AT approx. +45°. Incomplete RBBB?	Acute, diffuse, moderately severe (+ + +) myocarditis, with degenera- tive changes of myocardial fibers; various myocardial fibers with <i>S.</i> <i>cruzi</i> . Edema of intima of anterior coronary artery	Chagasic encephalitis; pas- sive congestion of lungs, liver, and spleen; fat de- generation of liver
10 2284 J.T.M.	2 yrs. 6 mos. M	2 mos.	Congestive heart fail- ure	—	Abnormal: Low voltage of QRS in extremity leads; left axis devia- tion	Acute very severe (+ + + + +), focal and diffuse myocarditis with rela- tively few <i>S. cruzi</i> in myocardial fibers; acute pericarditis over basal portion of left ventricle	Passive congestion of lungs, liver, spleen, and kid- neys; fat degeneration of liver; lymphoid hyper- plasia of spleen
11 1500 Ub C.S.	15 mos. F	40 days	Congestive heart fail- ure	—	—	Acute, very severe (+ + + + +), diffuse myocarditis with many myocardial fibers parasitized with <i>S. cruzi</i> ; circum- scribed acute pericarditis at base of right ventricle	Passive congestion lungs, liver, and spleen; fat de- generation of liver.

* In cases 5 and 6 autopsy was performed by Dr. Torres and Dr. Duarte, Division of Pathology, Instituto Oswaldo Cruz; in the remaining cases only the heart and fragments of some organs were available for microscopic examination.

mortem examination leaves the impression that in most if not in all these cases, the heart lesions were essentially autopsy findings whose full clinical importance would hardly be appreciated during life. An acute, severe, diffuse myocarditis with leishmanial forms of *S. cruzi* in myocardial fibers was present in all the 19 autopsy cases from the literature, and in most of them there were also abundant pericardial transudate and signs of passive congestion in various organs. Specific inflammatory lesions of the central nervous system (acute meningoencephalitis) were also found in several of these 19 cases.

In our own series of 11 autopsy cases of acute Chagas' disease from Bambuí (table 1) the chief anatomic findings were similar to

those of the 19 previously reported cases: acute myocarditis (fig. 4) with *S. cruzi* in myocardial fibers in all the 11 cases; anatomic evidences of circulatory failure in 8 cases; chagasic encephalitis in 2 cases (the nervous system was not examined in the remaining cases); pronounced fatty degeneration of the liver in 7 cases.

With the exception of the frequency and severity of the heart lesions, the manifestations of acute Chagas' heart disease do not differ essentially from those due to acute myocarditis of other etiologies.

In severe cases the picture of bilateral heart failure (pulmonary and systemic congestion, bilateral increase of cardiac shadow, regular heart rhythm, accelerated heart rate, gallop

FIG. 4. Acute myocarditis: A. Case no. 11 (table 1). Patient aged 15 months. Acute myocarditis of approximately 40 days' duration. The muscle fibers are separated by a diffuse infiltration of mononuclear cells (H & E $\times 200$). B. Case no. 8 (table 1). Patient aged 2 years. Myocarditis of approximately 6 months' duration. Diffuse inflammatory infiltration, loss of muscle substance and some degree of proliferation of the interstitial connective tissue (H & E $\times 220$). C. Same patient as in B. The cellular exudate consists of lymphocytes, monocytoïd cells, and histiocytes. One myocardial fiber is seen (arrow) with leishmanial forms of *S. cruzi* (H & E $\times 440$).

FIG. 5. Acute Chagas' heart disease. Case no. 1833. Marked enlargement of the cardiac shadow, particularly to the left, in the sixth week of infection. Primary T-wave changes. The cardiac shadow and the electrocardiogram reverted to normal at the fourth month of infection.

rhythm or embryocardia (tic-tac rhythm), decreased systolic and low pulse pressure with small radial pulse) allows the clinical diagnosis of myocarditis to be made without difficulty. The convulsive syndrome frequently exhibited by children with severe forms of the disease may be in some cases related to acute circulatory failure.

In mild cases detection of the acute myocarditis by physical examination is less accurate; gallop rhythm with diminution of the intensity of the first heart sound (delayed A-V conduction time) and signs of cardiac dilatation may be the only reliable physical signs of myocardial involvement. Serial x-ray examination of the chest and electrocardiography are the most accurate methods for detecting acute Chagas' heart disease. Enlargement of the cardiac shadow is present in the majority of patients with acute Chagas' disease. It is diffuse and may be moderate or pronounced (fig. 5). The

form and the variations in the size of the cardiac shadow suggest that pericardial effusion is often an important factor in the increased cardiac shadow.¹³ Usually the cardiac silhouette returns to normal earlier than the electrocardiogram.

Electrocardiographic abnormalities were present in 78 (43.3 per cent) of a group of 180 (159 nonfatal and 21 fatal) patients with acute Chagas' disease. The most common electrocardiographic changes in the entire group of cases of acute Chagas' disease (table 2) were prolongation of P-R interval, primary T-wave changes, low voltage of QRS, prolongation of Q-T interval, and associated ST-T changes ("injury-ischemia pattern").

Comparing the findings in the nonfatal (159 cases) and in the fatal group (21 cases, 11 with postmortem examination) of patients (table 2) the following observations may be made.

TABLE 2.—*Electrocardiographic Changes in 180 Patients (159 Nonfatal and 21 Fatal) with Acute Chagas' Disease*

	Nonfatal: 159 patients		Fatal: 21 patients		Total: 180 patients	
	No. of cases*	%	No. of cases*	%	No. of cases*	%
Abnormal electrocardiogram.....	60	37.7	18	85.7	78	43.3
Prolongation of P-R....	32	20.1	7	33.3	39	21.7
Primary T-wave changes	28	17.6	7	33.3	35	19.4
Prolongation of Q-T interval.....	12	7.5	1	4.7	13	7.2
ST-T changes (injury-ischemia pattern).....	4	2.5	4	19.0	8	4.4
Low voltage of QRS....	7	4.4	8	38.1	15	8.3
P-wave abnormalities....	4	2.5	1	4.8	5	2.8
Ventricular extrasystoles	3	1.9	1	4.8	4	2.2
Nodal rhythm.....	1	0.6	—	—	1	0.5
RBBB, complete.....			2	9.5	2	1.1

* Two or more types of electrocardiographic changes were frequently present in the same patient.

1. Myocardial damage was detected by the electrocardiogram in a high (85.7 per cent) percentage of cases from the fatal group. In the nonfatal group only 37.7 per cent showed electrocardiographic abnormalities.

2. Prolongation of P-R interval and primary T wave changes were frequent in the nonfatal group, but had a significantly higher (33.3 per cent) incidence in the fatal group.

3. S-T displacements associated with T-wave changes ("injury-ischemia") and low voltage of QRS were uncommon in the nonfatal and had a significantly high incidence in the fatal group.

4. The only 2 cases of intraventricular block (right bundle-branch block) were in the fatal group.

A comparison of tables 2 and 3 calls attention to the marked differences in the type and incidence of electrocardiographic abnormalities in acute and chronic Chagas' heart disease. Also from the clinical and pathologic standpoints, acute and chronic Chagas' heart disease each have quite distinctive features. As a matter of fact, these 2 types of heart disease seem to have in common only the etiologic agent and a widespread inflammatory process of the myocardium.

The diffuse myocardial lesions in acute Chagas' disease tend to alter the ventricular complex and cause only minor degrees of A-V conduction disturbances. They are usually not apt to produce marked conduction disturbances nor to set up frequent ectopic contractions. Electrocardiographic-anatomic correlations in our human and experimental material indicate that the spread of excitation to the atria and ventricles is apparently not significantly disturbed despite the severe, diffuse, acute inflammatory myocardial lesions; only when dilatation of heart cavities or proliferation of interstitial connective tissue takes place do significant conduction disturbances appear. The appearance of intraventricular block (right bundle-branch block) in acute Chagas' heart disease carries a poor prognosis; in our human and experimental material this disturbance occurred only in cases of severe myocardial lesions and cardiac dilatation. A quite different prognostic significance is attached to right bundle-branch block in chronic Chagas' heart disease; in this condition the conduction disturbance may be found in cases showing only limited cicatricial inflammatory myocardial lesions without cardiac enlargement, and may be compatible with long survival of the patient.

Diagnosis

Laboratory diagnosis of acute Chagas' disease is based on the demonstration of the parasite. In the first weeks of infection the high level of parasitemia permits demonstration of circulating forms (trypanosomes) of *S. cruzi* in a fresh blood smear or a thick drop preparation of blood. As the infection evolves, the number of blood circulating trypanosomes decreases; after the sixth to tenth weeks of infection direct microscopic demonstration of the parasite in the blood is difficult. At this time, xenodiagnosis,* animal inoculation of blood, or blood culture are the recommended procedures for demonstration of the parasite. A precipitin reaction proposed by Muniz and

* A diagnostic method proposed by Brumpt, consisting in feeding uninfected laboratory-bred triatomid bugs on patients and examining the bugs' feces for the presence of *S. cruzi* 2 to 3 months after feeding.

TABLE 3.—*Electrocardiographic Changes in 683 Patients with Chronic Chagas' Heart Disease (Including 200 Fatal Cases)*

	Non fatal: 483 patients		Fatal: 200 patients		Total: 683 patients	
	No. of cases*	%	No. of cases*	%	No. of cases*	%
Atrial-ventricular block.....	174	36.0	74	37.0	248	36.3
First degree A-V block.....	138	28.6	30	15.0	168	24.6
Second degree A-V block.....	14	2.9	10	5.0	24	3.5
Complete A-V block.....	22	4.5	34	17.0	56	8.2
right BBB type of QRS.....	14	2.9	27	13.5	41	6.0
left BBB type of QRS.....	2	0.4	—	—	2	0.3
indeterminate BBB type of QRS.....	3	0.6	1	0.5	4	0.6
right and left BBB type of QRS.....	1	0.2	6	3.0	7	1.0
normal duration of QRS.....	2	0.4	—	—	2	0.3
Intraventricular block.....	254	52.6	128	64.0	382	55.9
Complete RBBB.....	226	46.8	104	52.0	330	48.3
type:						
concordant.....	43	8.9	23	11.5	66	9.7
S-wide.....	128	26.5	29	14.5	157	23.0
discordant.....	44	9.1	26	13.0	70	10.2
"atypical".....	11	2.3	26	13.0	37	5.4
associated with QRS changes in lead I or left precordial leads						
Slurring of R; delayed intrinsicoid deflection.....	6	1.2	21	10.5	27	3.9
Signs of left ventricular enlargement.....	2	0.4	8	4.0	10	1.5
Signs of necrosis of anterior wall.....	6	1.2	25	12.5	31	4.5
associated with ST or T wave changes.....	27	5.6	39	19.5	66	9.7
Incomplete RBBB (nonisolated).....	18	3.7	4	2.0	22	3.2
Complete LBBB.....	6	1.2	9	4.5	15	2.2
Incomplete LBBB.....	4	0.8	11	5.5	15	2.2
QRS-T changes without intraventricular block						
Signs of left ventricular enlargement.....	11	2.2	13	6.5	24	3.5
Isolated QRS changes.....	33	6.8	29	14.5	62	9.1
Primary ST-T changes.....	62	12.8	26	13.0	88	12.9
Abnormalities of P wave.....	27	5.6	46	23.0	73	10.7
Premature contractions.....	166	34.4	161	80.5	327	47.9
Supraventricular.....	11	2.3	8	4.0	19	2.8
Ventricular.....	153	31.7	138	69.0	291	42.6
Extrasystolic ventricular tachycardia.....	2	0.4	15	7.5	17	2.5
Paroxysmal tachycardia.....	3	0.6	13	6.5	16	2.3
Supraventricular.....	1	0.2	1	0.5	2	0.3
Ventricular.....	2	0.4	12	6.0	14	2.0
Atrial fibrillation or flutter.....	13	2.7	32	16.0	45	6.6
Nodal rhythm, Isorhythmic A-V dissociation.....	2	0.4	4	2.0	6	0.9

* Two or more types of electrocardiographic changes were frequently present in the same patient.

Freitas²⁴ has shown consistently positive results in our acute cases. Complement-fixation test (Guerreiro-Machado's reaction) may yield negative results in the early stages of acute infection; it is a valuable procedure for the diagnosis of chronic Chagas' disease.

Mortality

Mortality during the acute period of Chagas' disease in 235 cases from Bambuí reached 9.4 per cent (22 cases). Death is due to congestive heart failure, convulsive seizures, or to associated infection. The acute infection is more severe in early infancy; in adolescents and adults it is rarely fatal.

Chagas' disease has a protracted course. The acute period gradually passes over into the chronic stage of the disease.¹³ The acute manifestations subside, but the patient remains infected, possibly for the rest of his life. In endemic areas, patients are subject to repeated reinfections. It is not known whether or not such reinfections play any role in the course of the disease. We know that patients kept away from endemic areas for many years remain infected and that the chronic heart involvement may progress.

In most cases the manifestations of acute Chagas' heart disease disappear in a few months or years.¹¹⁻¹³ Some patients may show residual electrocardiographic abnormalities. From a group of 72 cases of acute Chagas' heart disease, followed from 4 to 10 years (average: 7 years, 5 months) in Bambuí, 11 patients (15.3 per cent) showed electrocardiographic abnormalities (9 with prolongation of P-R). It seems probable that such electrocardiographic changes represent active myocarditis (in 1 patient incomplete right bundle-branch block changed to complete right bundle-branch block) but no anatomic studies are as yet available from this group of cases.

ASYMPTOMATIC PERIOD OF CHRONIC INFECTION

Subsidence of the clinical manifestations and reduction of the number of trypanosomes in the blood to such levels that they can no longer be seen on direct fresh examination are the usual criteria for distinguishing the acute from the chronic stages of the disease.

The asymptomatic period, described¹³ as the chronic indeterminate form of the disease, comprises a long period, usually from 10 to 20 years, between the end of the acute stage and the establishment of the late heart disease of chronic infection. Patients during the asymptomatic period may be considered as belonging to the category of potential cardiac disease.

In the first years following the acute infection, these patients show some degree of enlargement of the superficial lymph nodes, occasionally moderate enlargement of the liver, as well as periods of slight, irregular elevations of temperature, increased blood sedimentation rate, and moderate lymphocytosis. In other cases the infection seems to remain mostly inactive for long periods of time.

Transition from the asymptomatic phase to the stages of heart disease in chronic infection is sometimes difficult to define clearly, since many patients develop transient electrocardiographic changes long before the appearance of the permanent cardiac manifestations of chronic Chagas' heart disease. From a group of 75 patients with a known acute period of infection (40 with normal electrocardiogram), 17 (22.7 per cent) developed electrocardiographic abnormalities during an average observation period of 10 years after the acute infection; the electrocardiographic changes were transient in 5 and permanent in 12.

In the endemic areas this group of asymptomatic chronic infection is the largest of the 3 groups of patients with *S. cruzi* infection. Although these patients are apparently healthy and asymptomatic, they are most important from the epidemiologic standpoint.

Age and Sex

There was no significant variation in the incidence of chronic infection according to sex in the entire group of 1,340 patients (males 650, females 690). Two thirds of the cases were between 11 and 40 years of age; 83.5 per cent were between 11 and 50 years (fig. 6). A significant preponderance of females (60.1 per cent) was observed in a group of 657 patients (females 390, males 267) (fig. 7) in the chronic asymptomatic stage of infection. In this group 83.6 per cent of the patients were in the

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FIG. 6. Age and sex distribution of 1,340 cases of chronic *S. cruzi* infection (683 with heart involvement and 657 without evidences of heart disease).

FIG. 7. Age and sex distribution of 657 cases of chronic *S. cruzi* infection without evidences of heart involvement.

FIG. 8. Incidence of heart involvement according to sex in different age groups of 1,340 patients with chronic *S. cruzi* infection.

FIG. 9. Age distribution of 683 cases of chronic Chagas' heart disease.

age groups from 11 to 50 years, the highest number of cases (51.2 per cent) being between 11 and 30 years of age.

CHRONIC CHAGAS' HEART DISEASE

From a medical point of view it may be stated that a clinical diagnosis of chronic *S.*

cruzi infection in man rests on the recognition of chronic Chagas' heart disease.

Incidence

During the period 1943-1955, approximately 2,100 chronic and 280 acute cases of Chagas' disease were diagnosed in Bambuí, Minas

Gerais. From the group of 1,340 chronic cases in which electrocardiograms were recorded, 683 (50.9 per cent) patients showed evidences of myocardial damage. Since 1945, when we reported¹⁰ our first cases, up to the present time approximately one half of the patients with chronic *S. cruzi* infection showed evidence of heart damage. The sample is not an unselected one, for many cardiac patients seek medical care in our Department. A survey made¹⁸ in the unselected population from 5 to 60 years of age in the same endemic area disclosed an incidence of 32.7 per cent of chronic heart damage in the group with chronic *S. cruzi* infection. Many cases of severe chronic Chagas' heart disease have been reported recently by various authors from the States of Minas Gerais, São Paulo, Bahia, Goiás, and Pernambuco, as well as from Argentina, Venezuela, and Educador. Variations seem to occur in the incidence and severity of myocardial damage in chronically infected patients from different endemic areas.¹³⁻¹⁵

Age and Sex

A progressive increase in incidence of heart involvement in different age groups of 1,340 patients with chronic *S. cruzi* infection was observed (fig. 8).

In this same group of patients, heart damage showed variations in its incidence according to sex in the different age groups (fig. 8): the males were preponderant in the age groups 11 to 50 and the females were slightly preponderant in the age groups up to 10 and over 61 years of age.

In the group of 683 cardiac patients, 383 (56 per cent) were males and 300 (44 per cent) were females.

Figure 9 shows that 82 per cent of the patients with chronic Chagas' heart disease are in the age groups from 11 to 50 years and that two thirds of these cases are between 11 and 40 years of age. There are a few cases under 10 and over 50 years of age.

From figures 3, 7, and 9 it will be observed that acute infection occurs in the first decade, the chronic asymptomatic cases are preponderant in the second and third decades, and that chronic Chagas' heart disease has its

highest incidence in the third and fourth decades of life.

Symptoms and Signs

The manifestations of chronic Chagas' heart disease depend mainly on the severity of the myocardial lesions, on the presence of heart failure, and on the type of arrhythmia.

In the early stages of chronic myocardial damage the patient may have no symptoms and the cardiac shadow may be normal or only slightly enlarged. In such patients, who are usually in the first or second decades of life, the diagnosis of the heart disease rests mainly on the electrocardiographic abnormalities.¹⁰ Even severe heart disease, manifested by cardiac enlargement and advanced degrees of A-V or intraventricular block or other electrocardiographic abnormalities, may be unaccompanied by symptoms. One is impressed in some cases by the scarcity of subjective manifestations in contrast with the severity of the objective signs of advanced heart disease.

Cardiac failure usually assumes the type of right and left ventricular failure, with pronounced systemic congestion. A predominantly right-sided type of heart failure with functional tricuspid regurgitation is frequently observed in patients with advanced congestive failure. Isolated left ventricular failure may be present, however, in the early stages of heart failure.

Physical examination shows irregularities of cardiac rhythm usually due to ventricular premature contractions or A-V block, signs of enlargement of the heart (due mainly to dilatation), and evidences of passive congestion (usually more pronounced in the systemic circulation).

Reduplication of the second pulmonic sound is commonly heard. Gallop rhythm, a muffled first heart sound at the mitral area, and systolic murmurs due to functional mitral or tricuspid regurgitation may be present in patients with congestive heart failure. Marked increase of systemic venous pressure and pronounced enlargement of the liver with occasional pulsation are usual findings in these patients. Systolic blood pressure is normal or, more commonly, moderately lowered, and the

pulse pressure is usually reduced; the radial pulse is small and irregular.

Roentgenography

X-ray pictures of the chest show moderate to pronounced, diffuse enlargement of the cardiac shadow and evidences of passive congestion in the lungs. Pulmonary congestion in many cases is not marked. Clear pulmonary fields together with marked bilateral enlargement of the heart shadow (fig. 10) is a common finding in the chest x-ray of patients with advanced chronic Chagas' heart disease.

Electrocardiography

Recent advances in the knowledge of Chagas' heart disease are due mostly to the electrocardiographic studies during the last decade. The diagnostic value and several peculiar features of the electrocardiographic findings in chronic Chagas' heart disease have been established^{10, 12, 13} on the basis of analysis of data from comparatively large groups of patients. These findings have been extensively confirmed by various authors in studies of cases from different endemic areas.

The electrocardiographic abnormalities in a group of 683 patients with chronic Chagas' heart disease (table 3), from Bambuí, are similar to our previous findings. A great variety of electrocardiographic abnormalities are observed. Complete right bundle-branch block, partial and complete A-V block, ventricular premature contractions, QRS abnormalities or primary T-wave changes, and abnormalities of P waves were common findings. Two or more of these abnormalities were found in the same patient in approximately one third of the cases. On the other hand, ectopic atrial rhythms or contractions, complete left bundle-branch block, high voltage of QRS with or without secondary ST-T changes, and marked ST displacements (injury) were unusual findings. Only a small percentage of cases of advanced chronic Chagas' heart disease failed to show conduction disturbances or ventricular premature contractions.

A-V Block. A-V block was present in 36.3 per cent of the cases. Mild A-V block was more common (28.6 per cent) in the nonfatal than

FIG. 10. Case no. 2 (table 4). Patient aged 15. Marked, bilateral enlargement of cardiac shadow in chronic Chagas' heart disease. Clear pulmonary fields.

in the fatal (15.0 per cent) group of cases. First degree A-V block occurs chiefly in the early stages of chronic Chagas' heart disease,¹³ being observed preponderantly in the younger age groups: 72.4 per cent of the cases from the nonfatal group were under 30 years of age. It was the most common (55.2 per cent of the cases) electrocardiographic abnormality present in the age group 11 to 20 years in the 483 nonfatal cases. Intravenous administration of 1 mg. of atropine sulfate may temporarily restore the A-V conduction time to normal; ocular compression may increase the degree of A-V block, with appearance of dropped ventricular beats in patients in the younger age groups.

Chronic *S. cruzi* infection was by far the most common cause of advanced A-V block in patients under 50 years of age in the endemic area that we studied. A comparatively high incidence of advanced A-V block was observed in chronic Chagas' heart disease¹⁰: second degree A-V block occurred in 3.5 per cent and complete A-V block in 8.2 per cent of the cases from the entire group of 683 patients with chronic Chagas' heart disease. A particularly high incidence (17 per cent) of complete A-V block was found in the group of 200 fatal cases. Ninety per cent of the cases of complete A-V block from this group were 21 to 50 years of

FIG. 11. Atypical type of right bundle-branch block, with slurred QRS and delayed intrinsicoid deflection in left precordial leads. From Dias and associates.¹⁰ Case no. 247. Aged 60. Aortic and coronary atherosclerosis. Chronic myocarditis (*S. cruzi* not found). Positive complement-fixation test for Chagas' disease. Autopsy: heart weight 520 Gm.; marked dilatation of all cardiac cavities; left ventricular thickness 12 mm. at base and 1 mm. at apex; mural thrombus, endocardial fibrosis, and pseudoaneurysm at the apex of left ventricle; diffuse mononuclear infiltration and fibrosis of myocardium, more severe in the left ventricle.

age. Normal duration of QRS is unusual in cases of complete A-V block; most cases have a widened and slurred QRS of the right bundle-branch block type, sometimes with high voltage.

Right Bundle-Branch Block. This is the most frequent conduction disturbance in chronic Chagas' heart disease.^{10, 12} The high incidence of right bundle-branch block contrasts with the rarity (2.2 per cent) of complete left bundle-branch block. The presence of complete right bundle-branch block in patients under 50 years of age from endemic areas has a high diagnostic value.¹³ In the endemic area that we studied, Chagas' disease was by far the most common cause of right bundle-branch block. In the nonfatal group right bundle-branch block was found in patients from 6 to 65 years of age, but 88 per cent of the cases were in the age groups 11 to 50 years. The incidence was only slightly higher in the fatal (52.0 per cent) than in the nonfatal (46.8 per cent) group of cases. However, some types of right bundle-branch block had a markedly different incidence in the 2 groups of cases: the wide S type (types 2 and

3) was more common in the nonfatal (26.5 per cent) than in the fatal (14.5 per cent) group, while concordant (type 1) and discordant (types 4 and 5) types were slightly, and the *atypical* type of right bundle-branch block (fig. 11) distinctly more frequent in the fatal than in the nonfatal group of cases. The Rs or qR type of QRS in lead I in the *atypical* type of right bundle-branch block may be changed to a qRS type when the record is made with the patient lying on his right side. Association of right bundle-branch block with conspicuous slurring of R deflection and delayed intrinsicoid deflection, or with a qR type of QRS and high R waves in left precordial leads, was more common in the fatal group of cases. These QRS changes are mostly found in patients over 40 and may in some cases be related to predominant left ventricular enlargement and fibrosis (cases 20, 21, table 4). QRS changes suggesting an anterior wall area of myocardial necrosis (usually in leads V₃, V₄, V₅) was a fairly frequent finding in the fatal group (fig. 12). Three patients with such QRS changes had an area of thinning of the cardiac wall at

the apex of left ventricle (cases no. 15, 17, 18), but in 3 other cases with similar electrocardiographic changes myocardial thinning was not found (cases no. 5, 10, 19, table 4). The typical pattern of myocardial infarction may occasionally be found (fig. 13). On a basis of morphologic analysis of the electrocardiogram, primary abnormalities of the final phase of the ventricular complex was diagnosed in 5.6 per cent of cases in the nonfatal and in 19.5 per cent of cases of the fatal group. It was not possible to exclude digitalis effect in several such cases.

QRST Changes without Intraventricular Block. This group includes chiefly patients of the more advanced age groups in whom no adequate electrocardiographic studies were made. Absence of intraventricular block was found in 44 patients (22 per cent) out of the 200 fatal cases; 11 such cases presented A-V block, without intraventricular block; the remaining 33 patients showed no type of heart block. If the cases in which more than 1 year elapsed between the last electrocardiogram and death of the patient are excluded, only 12 cases (6 per cent) remain in the group without heart block. Nevertheless it may be concluded that the absence of conduction disturbances in fatal cases of chronic Chagas' heart disease is quite uncommon.

Premature Ventricular Contractions. These are common in chronic Chagas' heart disease and were observed in 69.0 per cent of the patients in the fatal group. They are frequently bigeminal, independent of digitalis effect, and commonly multiple and polytopic and increased in number by effort. Runs of ventricular extrasystoles forming bouts of extrasystolic ventricular tachycardia (fig. 14) are seen in patients with advanced heart disease, particularly when under digitalis therapy. More prolonged attacks of ventricular paroxysmal tachycardia may appear spontaneously or under the influence of effort. Patients showing polytopic ventricular premature contractions are prone to sudden death. Digitalis should be employed cautiously.

Abnormalities of P Waves, Atrial Fibrillation or Flutter. A high incidence of marked abnormalities of P waves (23 per cent) and of atrial

fibrillation or flutter (16 per cent) was observed in the fatal group of cases, in contrast with the low incidence of these changes in the nonfatal group. The severe prognostic significance of atrial fibrillation in chronic Chagas' heart disease was pointed out by Chagas.^{5,7} Its incidence is higher in the older age groups, but its severity is greater in young patients.

In the autopsy series (table 4) there were 8 patients with marked abnormalities of P waves and 6 patients with atrial fibrillation or flutter. No correlation was found between these electrocardiographic changes and the presence of atrial thrombosis or pulmonary infarcts. Cardiac enlargement was present in all the cases but varied greatly. Congestive heart failure was present in all cases.

Diagnosis

Consideration of the possibility of Chagas' disease in young or middle-aged patients who have been infected with *S. cruzi* in endemic areas of the disease and who present a chronic nonvalvular type of heart disease is the first prerequisite for a correct etiologic diagnosis.

The clinical history is of utmost importance. Detailed information should be obtained on epidemiologic factors operating in the area where the patient was born or has lived (existence of the insect vectors, the type of house the patient has inhabited, the presence of bugs in the house, etc.). A history of heart disease with congestive failure or sudden death in other members of the same family or in other young individuals from the same region is commonly elicited. Patients with the chronic type of heart disease rarely give a clear history of the initial stage of the infection, for this usually occurs in the first years of life. A complement-fixation test for Chagas' disease should be made in any young or middle-aged patient from endemic areas of the disease presenting a myocardial type of heart disease, with conduction disturbances, ventricular premature contractions, diffuse enlargement of the heart, with or without manifestations of congestive heart failure. Complete right bundle-branch block and complete A-V block (usually associated with ventricular premature contractions) in patients under 50 years, from endemic

TABLE 4.—*Clinicopathologic Findings in Twenty-One Cases of Chronic Chagas' Heart Disease with S. Cruzi in Myocardial Fibrosis*

Case, reg. no.	Age (years) and sex	Clinical findings	Anatomic findings*
1 222	6 F	CHF 25 days; acute infection probably occurred 3 years ago; Enlarged superficial lymph nodes; sinus tachycardia; AQRS +60°; low voltage slurred QRS standard leads; prolonged Q-T interval; AT -60°; isoelectric T in V ₄ , V ₅	Chronic, diffuse and focal myocarditis, extensive areas fibrosis; preponderantly subendocardial; endocardial thickening base of left ventricle; CPC lungs, liver, spleen, and kidneys; fat degeneration liver
2† 1,847	15 M	CHF 1 year; marked, bilateral cardiac enlargement. ECG: atrial fibrillation and flutter, complete A-V block, multiple, polytopic ventricular extrasystoles, paroxysmal ventricular tachycardia	HW: 665 Gm.; H & D; aneurysm apex of left ventricle; chronic, diffuse and focal myocarditis; circumscribed pericarditis base left ventricle; moderate intimal hyperplasia small and medium-sized branches coronary arteries; CPC lungs, liver, spleen, and kidneys
3† 160	22 M	CHF 5 years; Adams-Stokes seizures; marked, bilateral cardiac enlargement; ECG: complete A-V block	HW 720 Gm.; H & D, marked; thrombosis right atrial appendage; endocardial fibrosis base left ventricle; chronic myocarditis, ventricles; infarct base of right lung; CPC lungs, liver, spleen, kidneys; medial hypertrophy small intramyocardial arteries; intimal proliferation and edema media of medium-sized coronary arteries
4 193	20 F	CHF 6 months. Functional mitral and tricuspid regurgitation; probable thyrotoxicosis; marked, bilateral enlargement heart. ECG: polytopic, multiple ventricular extrasystoles, runs of paroxysmal ventricular tachycardia, low voltage QRS in standard leads, negative T in L ₂ , L ₃ , V ₅ , V ₆ , notched R deflections in V ₅ , V ₆	HW 400 Gm.; H & D; mural thrombus and small area thinning apex left ventricle; severe, diffuse, chronic and subacute myocarditis; granulomatous formations with multinucleated giant cells in ventricular myocardium; circumscribed pericarditis base left ventricle; areas infiltrative endocarditis; CPC lungs, liver, spleen, kidneys
5† 1,780	21 M	CHF 8 months; marked, bilateral enlargement cardiac shadow; sudden death; ECG: frequent, polytopic ventricular extrasystoles; prolonged P-R.; type IV RBBB; small R in V ₃ , V ₄	HW 510 Gm.; H & D; chronic myocarditis, with granulomatous formations in right atrium and ventricle; CPC lungs, liver, spleen, kidneys; anasarca; left pulmonary (base) and splenic infarcts; pulmonary tuberculosis; tuberculous lymphadenitis at hilum; miliary tuberculosis spleen
6 1,918	26 M	CHF 7 months; precordial pain on effort; moderate bilateral enlargement of cardiac shadow; ECG: widened notched P waves, multiple, polytopic ventricular extrasystoles, low, slurred QRS in standard leads, AQRS -75°, slurred R in V ₅ , V ₆ , QRS-T changes suggesting anterolateral infarction, QS in L ₂ , L ₃ , V ₄ , V ₆ (posterior necrosis?); cardiopasm	HW 390 Gm.; H & D; moderate; extensive mural thrombosis apex left ventricle with marked, local endocardial fibrosis; chronic and subacute diffuse myocarditis, preponderantly left ventricle; epicarditis base left ventricle; fat degeneration liver; CPC lungs, liver, spleen, kidneys
7† J.D.M.	26 M	CHF 8 months; repeated pulmonary embolism; marked, bilateral enlargement heart; ECG: sinus tachycardia, rate 150, polytopic ventricular extrasystoles, incomplete left bundle-branch block	HW 600 Gm.; H & D; thrombosis apex left ventricle and right atrial appendage; chronic, diffuse myocarditis, more severe left ventricle; multiple, bilateral pulmonary infarcts; CPC lungs, liver spleen, kidneys; anasarca
8† 180	28 M	Several bouts CHF last 6 years; Adams-Stokes seizures; marked, bilateral enlargement of cardiac shadow; ECG: complete A-V block, multiple, polytopic ventricular extrasystoles, atrial fibrillation	HW 750 Gm.; marked H & D; aneurysm apex left ventricle; mural thrombus apex left ventricle; in right atrium and small thrombus base of left and right ventricles; endocardial fibrosis apex left ventricle and base both ventricles; chronic diffuse myocarditis, more severe left ventricle; intimal hyperplasia main branches coronary arteries; hypertrophy media of small intramyocardial arteries; CPC lungs, liver, spleen, kidneys; anasarca

9† 1.730	30 M	CHF 2 years; marked, bilateral enlargement heart; death due to pulmonary embolism; ECG: second degree A-V block, multiple, irregular, polytopic ventricular extrasystoles, abnormal P waves, type IV of RBBB, QS in V ₄	HW 500 Gm.; H & D; chronic diffuse myocarditis; aortic atherosclerosis (mild); multiple bilateral pulmonary infarcts; splenic and renal infarcts; CPC lungs, liver, spleen, kidneys; anasarca
10 569	27 F	Death, congestive heart failure; ECG: atrial fibrillation, type IV RBBB, qR in V ₄ , W-shaped in V ₄ , and rS in V ₅	HW 370 Gm.; H & D: small thrombus apex left ventricle without local thinning of cardiac wall; thrombosis right atrial appendage; chronic diffuse myocarditis with areas subacute inflammation, moderate intimal thickening small branches coronary arteries; CPC lungs, liver, spleen, kidneys
11† 417	35 M	CHF 2 years; marked, bilateral enlargement heart; sudden death; ECG: complete A-V block, frequent, polytopic, ventricular extrasystoles, atrial fibrillo-flutter last 3 weeks	HW 400 Gm.; H & D; thrombosis apex left ventricle; chronic diffuse myocarditis; moderate atherosclerosis aorta, coronary and cerebral arteries; pulmonary emphysema; old pulmonary and kidney infarcts; area cerebral softening left hemisphere involving temporal lobe; CPC liver, spleen
12 307	38 M	CHF 6 months; ECG: abnormal P waves, polytopic ventricular extrasystoles, incomplete left bundle-branch block	HW 480 Gm.; H & D; thrombosis apex left ventricle with local thinning cardiac wall; thrombosis right atrium; areas fibrous thickening endocardium, apex and base left ventricle, base right ventricle, and right atrium; severe, diffuse, chronic and subacute myocarditis, preponderantly left ventricle; moderate, diffuse, intimal hyperplasia main branches coronary arteries; CPC lungs, liver, spleen, kidneys
13 1.858	39 M	CHF 18 months; marked, bilateral enlargement heart; ECG: abnormal P waves, polytopic ventricular extrasystoles, deep S in V ₂ and high R in V ₆ , V ₈ , QRS-ST/T changes suggesting recent high anterolateral infarction	HW 500 Gm.; H & D; preponderantly left ventricle; thrombosis at right atrial appendage; chronic myocarditis, preponderantly left ventricle; CPC lungs, liver, spleen, kidneys
14† 184	40 M	CHF 3 years; Adams-Stokes seizures; marked, bilateral enlargement heart; ECG: complete A-V block, ventricular extrasystoles	HW 540 Gm.; H & D; area endocardial fibrosis base of left ventricle; chronic, diffuse and focal myocarditis with granulomatous formations; intimal proliferation of coronary arteries with marked reduction of vascular lumen in some areas, CPC lungs, liver, spleen, kidneys
15† 198	43 M	CHF 20 months; attacks of paroxysmal tachycardia; syphilitic aortitis; marked, bilateral enlargement cardiac shadow, elongation and cylindric dilatation of aortic arch; terminal bronchopneumonia; ECG: multiple, polytopic ventricular extrasystoles, "concordant inverted" type of RBBB, QS in V ₄ , V ₅	HW 640 Gm.; H & D; endocardial fibrosis apex left ventricle with marked thinning of cardiac wall at this area; chronic diffuse myocarditis; myocardium at apex of left ventricle almost completely fibrosed; syphilitic and atherosclerotic lesions of aortic walls; mild intimal hyperplasia main branches coronary arteries; multiple bilateral pulmonary infarcts; bronchopneumonia; bilateral pachypleuritis; CPC lungs, liver, spleen, kidneys
16† 197	45 M	CHF 2 years; marked, bilateral enlargement cardiac shadow; pulmonary tuberculosis; cachexia; ECG: abnormal P waves, polytopic ventricular extrasystoles, concordant type of RBBB, wide and slurred Q deflection in L ₂ , L ₃ (posterior wall necrosis?)	HW 520 Gm.; H & D; endocardial thickening and mural thrombosis at apex and base of left ventricle and apex right ventricle; diffuse thickening of endocardium of right atrium; chronic myocarditis with granulomatous formations; extensive areas of subendocardial fibrosis left ventricle; mild myocardial lesions at atria and outflow tract of right ventricle; mild hyperplasia of intima of main coronary arteries; mild aortic atherosclerosis; caseous pulmonary tuberculosis; miliary tuberculosis of peritoneum, kidneys; CPC lungs, liver, spleen, kidneys

TABLE 4.—*Concluded*

Case, reg. no.	Age (years) and sex	Clinical findings	Anatomic findings*
17† 147	50 M	CHF 2 years; grossly irregular heart action with attacks of paroxysmal tachycardia; bilateral enlargement of the heart; chronic malaria; syphilis; aortic atherosclerosis; fibrosis upper lobe right lung (tuberculosis); ECG: atrial fibrillation, multiple, polytopic ventricular extrasystoles, runs of paroxysmal ventricular tachycardia, low voltage of QRST in standard leads, negative T waves in I ₂ , L ₄ , low R deflections in left precordial leads, transient, complete RBBB	HW 340 Gm.; H & D; moderate thinning apex left ventricle; chronic myocarditis, with extensive fibrosis particularly in left ventricle; mild aortic atherosclerosis; irregular hyperplasia intima of coronary arteries with severe reduction of lumen; atherosclerotic kidney disease with old infarcts; pulmonary fibrosis (tuberculosis?); CPC lungs, liver, spleen, kidneys; anasarca
18† 2,019	51 M	CHF 3 years; functional tricuspid regurgitation; atypical precordial pains; marked bilateral enlargement of the heart; aortic atherosclerosis; thrombophlebitis of lower extremities; multiple pulmonary embolism; cardiospasm; cachexia; ECG: partial A-V block, notched and widened P waves, type IV of RBBB, delayed R deflections in V ₄ , V ₆ , W type of QRS in V ₄ , multiple, polytopic ventricular extrasystoles, ventricular scapes	HW 500 Gm.; H & D; mural thrombosis apex left ventricle and right atrium; areas endocardial fibrosis at apex and base of left ventricle; thinning of cardiac wall at apex of left ventricle; chronic myocarditis; aortic and coronary atherosclerosis; atheromatous plaque at mitral valve; multiple infarcts at base of both lungs; multiple splenic infarcts; CPC lungs, liver, spleen, kidneys; anasarca; megasophagus and megacolon
19 249	55 F	CHF 1 year; ECG: atrial fibrillation, polytopic ventricular extrasystoles, low voltage of QRS in standard leads, RBBB, low R deflections in V ₄ , V ₆	Chronic myocarditis with focal and diffuse fibrosis preponderantly left ventricle, CPC lungs, liver, spleen, and kidneys
20† 199	56 M	CHF 3 years; marked bilateral enlargement of heart; aortic atherosclerosis; terminal bronchopneumonia; ECG: polytopic ventricular extrasystoles, abnormal P waves, incomplete RBBB with slurred R and delayed intrinsicoid deflection in V ₄ , V ₆ ; primary T wave changes (?)	HW 470 Gm.; H & D; preponderantly left ventricle; chronic myocarditis with diffuse fibrosis, preponderantly subendocardial areas of left ventricle; atheromatous plaque at left coronary artery with moderate reduction of the vascular lumen; CPC of lungs, liver, spleen, kidneys; anasarca; bronchopneumonia
21 1,341	58 M	CHF 4 years; moderate enlargement of cardiac shadow, predominantly left ventricle; aortic atherosclerosis; B.P. 140/90; ECG: frequent, polytopic ventricular extrasystoles, "atypical" RBBB, high, slurred R deflections in V ₄ , V ₆ , negative T waves from V ₁ to V ₆	HW 450 Gm.; H & D; preponderantly left ventricle; chronic myocarditis, preponderantly left ventricle; atherosclerosis coronary arteries; mild atherosclerosis renal arteries; chronic diffuse glomerulonephritis; CPC lungs, liver, and spleen

* Fragments from 8 to 14 different areas of the heart were examined.

† Autopsy performed by Dr. Torres and Dr. Duarte, Division of Pathology, Instituto Oswaldo Cruz. In the remaining cases only the heart and fragments of some organs were available for examination.

HW = heart weight; H & D = hypertrophy and dilatation; CPC = chronic passive congestion; CHF = congestive heart failure; Reg. No. = registration number

Complement-fixation test was positive in all cases. Xenodiagnosis was positive in cases 2, 7, 8, 9, 17, 19, 20, and 21; negative, in cases 1, 3, 4, 5, 6, 11, 12, 13, 14, 15, 16, 18.

FIG. 12. Right bundle-branch block with qR in V_3 , W shaped in V_4 , and rS type of QRS in V_5 , suggesting anterior necrosis. Case no. 10, table 4. Woman, aged 27. There was no local thinning of the cardiac wall at the apex of left ventricle. The myocardial lesions in this area were not more severe than in other areas of left ventricle.

areas of Chagas' disease, are more commonly associated with chronic Chagas' heart disease.

It may be assumed that a fairly characteristic clinical picture of the cardiopathy with a positive Guerreiro-Machado's reaction constitutes a sound basis for the diagnosis of chronic Chagas' heart disease, despite repeatedly negative results of xenodiagnosis.^{13, 15} In 13 out of the 21 cases of chronic Chagas' heart disease proved at autopsy, the diagnosis was made solely on a clinicoserologic basis. In 12 of these cases xenodiagnosis yielded negative results and in some of them repeatedly so. In the remaining 8 patients xenodiagnosis was

also positive. Very rarely the complement-fixation test may be negative and the xenodiagnosis may yield positive results.

In its early stages, chronic Chagas' heart disease, in patients under 20 years of age, may be difficult to differentiate from rheumatic carditis. Loud systolic murmurs due to functional mitral or tricuspid regurgitation in some cases of chronic Chagas' heart disease with advanced heart failure may lead to an erroneous diagnosis of valvular heart disease. Coronary heart disease is the most difficult problem in differential diagnosis. Chronic Chagas' heart disease occurs in the younger age groups,

FIG. 13. QRST changes without bundle-branch block. Case no. 6, table 4, aged 26. Marked left axis deviation, deep S in V_2 , slurred QRS with delayed intrinsicoid deflection in left precordial leads, suggesting left ventricular enlargement. QS in L_2 , L_3 , and V_F , suggesting posterior necrosis. QS in V_2 and qR from V_4 to V_6 , with ST-T changes, suggesting anterolateral infarction. There were severe chronic and subacute diffuse myocarditis with endocardial fibrosis and mural thrombosis at apex of left ventricle. The main coronary arteries were patent and no myocardial infarction was found.

the patients do not complain of the typical precordial pain; the acute, transient injury changes of the electrocardiogram are not common. In age groups over 50, coronary atherosclerosis is commonly associated with chronic Chagas' heart disease. High blood pressure is unusual in patients with chronic Chagas' heart disease.

At the present stage of our knowledge it seems reasonable to assume that in countries where Chagas' disease exists in an endemic form, such diagnoses as Fiedler's myocarditis, chronic myocarditis of unknown etiology, or myocardial disease of unknown cause should not be made unless Chagas' disease has been adequately excluded as a possible etiologic factor.

Clinical Course and Prognosis

As a rule the heart lesions of chronic *S. cruzi* infection develop and progress slowly.

Even after the manifestations of heart failure the patient may survive for a long time. Most cases exhibit several bouts of congestive heart failure until the condition finally becomes irreversible.

In some patients, usually under 30 years of age, the heart condition presents a brief, more severe course. Heart failure supervenes earlier and has no tendency to reversion. There are gross irregularities of cardiac rhythm (ventricular extrasystoles, ventricular tachycardia, atrial fibrillation) and abnormalities of QRS or T waves, without advanced heart block; death is due to congestive heart failure, usually with pulmonary embolism. In the myocardium there are acute and chronic inflammatory lesions; the fibrotic lesions are less marked and *S. cruzi* is usually found with less difficulty (cases 1, 4, and 6, table 4). Such cases could be classified as subacute Chagas' heart disease.

Approximately 55 per cent of the fatal cases

FIG. 14. Complex arrhythmias resulting in chaotic heart action. *A.* Case no. 4, table 4. Woman aged 20. Sinus rhythm; atrial rate 106. P-R = 0.16 sec. Multiple, polytopic premature ventricular contractions, forming bouts of extrasystolic ventricular tachycardia. The patient received small doses of digitalis; ectopic contractions disappeared with discontinuance of the drug. Record made 27 days before death of the patient. *B.* Case no. 1732. Man, aged 47. Atrial tachycardia, rate 187. Bouts of extrasystolic ventricular tachycardia. Record made 3 days before death of the patient. *C.* Case no. 2197. Woman, aged 38. Atrial fibrillation with runs of probably ectopic ventricular contractions (or transient left bundle-branch block of variable degrees?).

FIG. 15. Age and sex distribution of 200 fatal cases of chronic Chagas' heart disease.

are in the age groups 21 to 40 (fig. 15). Mortality is low in patients up to 20 years of age.

Prognosis is difficult. Sudden and unexpected death is very common in this cardiopathy. Patients with moderately advanced heart damage and without heart failure may die unexpectedly. Complete A-V block, some types of right bundle-branch block, frequent, polytopic ventricular premature contractions, ventricular tachycardia, QRS abnormalities suggesting an area of myocardial necrosis, marked enlargement of the heart, and signs of heart failure are of severe prognostic significance.

Pathology

The cardiac lesions of Chagas' disease were initially described by Vianna,²⁹ Chagas,^{5, 6} Torres,²⁶⁻²⁸ and Mazza¹⁹⁻²¹ in fatal cases of American trypanosomiasis. The chief anatomic findings included enlargement of all the cardiac cavities; hypertrophy of the heart; a diffuse inflammatory process of the myocardium (occasionally involving the parietal endocardium²⁸ with diffuse fibrosis and infiltration by lymphocytes, macrophages, and plasma cells, and in some cases eosinophils and polymorphonuclear neutrophils; areas of waxy degeneration of myocardial fibers and the presence of leishmanial forms of *S. cruzi* in myocardial fibers.

The condition has been described^{5, 6} as an isolated myocardial disease, without involvement of the valvular endocardium or the large vessels.

The number of published autopsy cases of chronic Chagas' heart disease with the presence of *S. cruzi* in the myocardium is small. The pathologic picture of this condition is still only incompletely known.

The chief clinicoanatomic findings in our series of 21 cases with the presence of *S. cruzi* in myocardial fibers are shown in table 4:

1. Heart weight was increased in all cases. Dilatation of all cardiac cavities was pronounced in most cases, particularly the right ventricle and the right atrium. Left ventricular thickness exceeded 15 mm. in 2 cases.

2. Circumscribed areas of endocardial fibrosis (fig. 16A) in the left ventricle were present in 15 cases, its localization being as follows: apex 8 cases, base 3 cases, apex and base 4 cases. In 3 of these cases there was also endocardial fibrosis at the apex (1 case) or base (2 cases) of the right ventricle.

Mural thrombus in different stages of organization (fig. 16B) at the apex of left ventricle was found in 11 cases. In 7 cases a circumscribed area of thinning of the apical portion of the left ventricle, constituting a pseudoaneurysm of the apex, was present. Mural thrombus at the right atrium or right atrial appendage was found in 7 cases, with endocardial fibrosis in 5.

3. A disseminated inflammatory process of the myocardium (fig. 16C) involving all the cardiac walls and septum, sometimes extending to the parietal endocardium, was found in all the 21 cases.

The cellular infiltration was diffuse and focal and consisted chiefly of lymphocytes, plasma cells, and macrophages; eosinophils and polymorphonuclear neutrophils were also present. In 4 cases the myocarditis could be classified as subacute (cases no. 4, 6, 10, 12). A "granulomatous form" of myocarditis was present in 5 cases (no. 4, 5, 11, 14, 16). Collections of lymphocytes and plasma cells in the epicardium (fig. 16D) were seen in some cases.

Focal and diffuse fibrosis of the myocardium was present in all cases, its intensity varying in different cases and in the same case from one

FIG. 16. Heart sections from patients with chronic Chagas' heart disease (table 4).

A. Case no. 1. Endocardial fibrosis. Note myocardial fibrosis at subendocardial areas (Masson stain $\times 54$). B. Case no. 16. Endocardial fibrosis and mural thrombosis in different stages of organization at apex of left ventricle (Masson stain $\times 54$). C. Case no. 6. Diffuse infiltration and fibrosis of myocardium. This aspect is seen in most sections of myocardium in cases of chronic Chagas' heart disease (H & E $\times 112$). D. Case no. 8. Collection of lymphocytes, macrophages, and plasma cells in epicardium (H & E $\times 112$). E. Case no. 4. A transverse section of a myocardial fiber containing leishmanial forms of *S. cruzi*. F. Case no. 4. Leishmanial forms of *S. cruzi* in myocardium phagocytosed by macrophages. Some polymorphonuclear cells are seen in the cellular exudate.

area to another. Fibrosis was conspicuously more severe in the left ventricle followed in order of frequency by the right ventricle and the right atrium. The less severe lesions were found in the left atrium. In 3 cases (no. 1, 16, 20) the fibrosis in the left ventricle was preponderantly subendocardial.

Leishmanial forms of *S. cruzi* in myocardial fibers (fig. 16E) were found in all the 21 cases; occasionally the parasite may be seen phagocytized by macrophages (fig. 16F). In 3 cases the parasite was found without difficulty on microscopic examination of the heart; in the remaining cases a time-consuming search was necessary. In no case was *S. cruzi* found in any other tissue but the myocardium.

4. Aortic and coronary atherosclerosis was conspicuous in the majority of the patients over 40 years of age. In some of them severe reduction of the lumen of the coronary arteries was present; in others the atherosclerotic lesions were mild.

Obliterative changes of the small and medium-sized branches of coronary arteries, with reduction of the vascular lumen, were present in various cases in the younger age groups. Thickening of the intima and edema or hypertrophy of the media was present in such cases.

Venous congestion and dilatation of capillaries, sometimes with extravasation of red blood cells into the myocardium, were found in most cases. Large thin-walled blood vessels, particularly in areas of extensive myocardial fibrosis, occasionally were observed.

5. Myocardial ischemia is probably an important mechanism in the development and progression of chronic Chagas' heart disease. In the enlarged heart, the vascular lesions and the dynamic factors usually operating in this condition (reduced systolic and pulse pressures, diminution of the capacity of the myocardium to raise systolic pressure, occurrence of frequent ectopic inefficient contractions) may result in coronary insufficiency. Local endocardial thickening, disturbed myocardial nutrition through the Thebesian vessels, and blood stagnation in the venous vessels of the heart have been claimed¹ to play major roles in the production of the ischemic myocardial lesions.

Treatment

No drug has yet been found to be entirely effective against *S. cruzi* infection. A 4-aminoquinoline derivative* and a sulfurated arsenobenzol† are claimed²² to possess trypanocidal effects on the circulating forms, but not on the intracellular forms of *S. cruzi* and to exert favorable effects on the evolution of some manifestations of the acute infection. Trials on experimentally infected dogs seem to show that a sulfurated arsenobenzol derivative‡ may destroy the blood forms of *S. cruzi* but does not prevent the development of chronic heart disease in these animals.¹⁶ Various other drugs have been tested¹⁶ without encouraging results.

SUMMARY AND CONCLUSIONS

Triatomid bugs, infected with *Schizotrypanum cruzi*, are widely distributed in this hemisphere, extending from the United States to Argentina. Our knowledge of the incidence and severity of human infection with *S. cruzi* in most of the large endemic areas is still incomplete. In the present state of our knowledge, Chagas' disease should be considered as an essentially cardiotropic infection, caused by *S. cruzi*, having an acute period with multiple, reversible manifestations due to involvement of various tissues and organs. The heart is affected in the majority of cases. A prolonged chronic course follows, with late manifestations of progressive heart involvement (chronic Chagas' heart disease). There is no definite proof as yet whether esophageal involvement (cardiospasm), which occurs so frequently in some endemic areas of Chagas' disease, is related to chronic *S. cruzi* infection.

Acute Chagas' heart disease may be defined as a reversible type of parasitic heart disease, caused by acute *S. cruzi* infection, occurring predominantly in infancy and childhood and anatomically characterized by an acute, diffuse, usually severe, specific myocarditis that eventually leads to heart failure without conspicuous irregularities of the cardiac rhythm.

* 7602 (Ac), Bayer

† 9736 (As), Bayer

‡ Spirotrypan (Farbwerke-Hoechst AG.)

Our present concept of chronic Chagas' heart disease is that of a progressive, usually severe type of heart disease, related to chronic *S. cruzi* infection, preponderantly affecting males in the 20- to 50-year age groups, manifested clinically by the almost constant occurrence of disturbances in the formation and conduction of the cardiac stimulus and by congestive heart failure. Anatomically widespread inflammatory changes of the myocardium are usually accompanied by circumscribed lesions of the parietal endocardium and by slowly developing ischemic myocardial changes.

SUMMARY IN INTERLINGUA

Scarabeos del genere *Triatoma*, inficite con *Schizotrypanum cruzi*, se trova extensamente distribuite in le Americas inter le Statos Unite e Argentina. Nostre cognoscentias del incidentia e del severitate de infectiones de humanos con *S. cruzi* in le majoritate del grande areas endemic es ancora incomplete. Super le base de nostre cognoscentias currente, morbo de Chagas debe esser considerate como un infection essentialmente cardiotropic, causate per *S. cruzi*, e characterisate per un periodo acute con multiple revertibile manifestationes que resulta del implication de varie histos e organos. Le corde es afficte in le majoritate del casos. Il seque un prolongate curso chronic, con tardive manifestationes de un progressive implication del corde (chronic morbo cardiac de Chagas). Il existe non ancora ulla prova definite que le implication esophagee (cardiospasmo), que occorre si frequentemente in certe areas endemic de morbo de Chagas, es connectite con infection chronic per *S. cruzi*.

Acute morbo cardiac de Chagas pote esser definite como un typo revertibile de parasitic morbo cardiac, causate per acute infection per *S. cruzi* occurrente predominantemente in infantes e juveniles, e characterisate anatomicamente per un acute, diffuse, e usualmente sever myocarditis specific que resulta in le curso del tempore in disfallimento cardiac sin conspicue irregularitates del rhythm cardiac.

Nostre currente concepto de chronic morbo cardiac de Chagas es le concepto de un progressive e usualmente sever type de morbo cardiac,

connectite con infection chronic per *S. cruzi*, afficte preponderantemente masculos del gruppos de etate inter 20 e 50 annos, e manifeste clinicamente per le quasi constante occurrentia de disturbance in le formation e le conduction del stimulo cardiac e per congestive disfallimento cardiac. Anatomicamente extense alterationes inflammatori del myocardio es usualmente accompagnate per circumscribite lesiones del endocardio parietal e per le lente disveloppamento de ischemic alterationes myocardial.

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Following his marriage Withering began to cast about for a more profitable practice since his income did not exceed £100 a year. When, therefore, he received an unexpected letter in February of 1775 from Erasmus Darwin telling him of the death of Dr. Small of Birmingham and suggesting that there was thus a good opening for a competent young practitioner in the busy Midland metropolis, he accepted the proposal with enthusiasm. Later in the year he was appointed a junior assistant to Dr. John Ash of the General Hospital. He started in practice in May and moved his family to Birmingham later in the year.

Withering's success in his new environment was immediate. Not only was he taken into social and intellectual circles, but his practice quickly grew to one bringing in an income of £1000 a year, later £2000, an enormous sum for those days—and this despite the fact that he held a daily free clinic for the poor at the General Hospital and is said to have treated three thousand cases annually without charge. He was sought as a consultant from all over the Midland and western counties. He also began to conduct a huge correspondence with distinguished personages who wrote for medical counsel. One such request came from Paris from no less a person than Benjamin Franklin who sought advice about treating his "bladder stone."

In the year 1785 Withering made a record of the distances he had travelled for consultation and found that it added up to 6,303 miles—not far perhaps for these days, but for the horsedrawn vehicles and bad country roads of the eighteenth century it was an astonishing feat. But the time was not wasted, for he occupied himself during his long journeys in making his clinical notes and examining specimens of his plants and minerals.—JOHN F. FULTON. *The Place of William Withering in Scientific Medicine*. J. Hist. Med. & Allied Sc., **8**: 8, 1953.

Comentários

Cardiopatía Chagásica: cinqüenta anos depois, um novo olhar

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Tarefa difícil a de analisar criticamente, mais de cinqüenta anos após sua publicação, um estudo que permanece como marco decisivo na fascinante trajetória médico-científica de cem anos de descoberta da doença de Chagas. Entretanto, dado o valor do trabalho que embasou tal publicação, revisá-lo, mesmo agora, ainda reúne vasto potencial de aprendizado e estímulo ao avanço dos conhecimentos de tão intrigante enfermidade. Mas é necessário ressaltar que essa trajetória iniciou-se de forma absolutamente singular na história da medicina. Em 1909, Carlos Chagas descrevia um novo agente mórbido, o *Trypanosoma cruzi*; o principal mecanismo de transmissão aos humanos, pela via vetorial; noções iniciais de sua imensa dimensão epidemiológica; e muito das manifestações clínicas de uma doença inteiramente desconhecida até então – a qual, longe de constituir raridade, afligia milhões de seres humanos (Chagas, 1909). Curiosamente, essa primeira publicação de Carlos Chagas não é citada no artigo de Francisco Laranja, Emmanuel Dias, Gerard Nóbrega e Aloisio Miranda (Laranja *et al.*, 1956). À parte alguns outros importantes desenvolvimentos científicos na década de 40, a publicação de Laranja e colaboradores pode ser considerada entre as mais expressivas contribuições científicas que culminariam no resgate da relevância médica e social da doença de Chagas, desde o relativo ostracismo em que permaneceu por algumas décadas. Aliás, os autores têm perfeita consciência dessa transição conceitual, quando ressaltam que “O conceito de doença de Chagas como uma rara afecção aguda era geralmente aceito”, porém “O real significado médico e social dessa infecção endêmica não era reconhecido”. Além de corretamente aplicada à situação então vigente, esta última constatação ainda se mostra tristemente verdadeira, com a doença relegada à categoria das negligenciadas pela comunidade médico-científica.

Também é impressionante verificar como, com poucas exceções, os conceitos emitidos pelos autores, com base em suas observações e descrições de milhares de pacientes, conti-

nuam a se mostrar válidos, mais de cinquenta anos após sua publicação. Uma dessas exceções reside na relutância em vincular à etiologia da doença de Chagas a ocorrência da esofagopatia, atribuída ao espasmo do cárdia. Em 1956, havia apenas a sugestão dessa associação etiológica, quando se dizia que “até 97% dos pacientes com cardioespasmo em certas áreas do Brasil também possuíam sorologia positiva para a presença do *T. cruzi* (reação de Guerreiro-Machado) e mesmo alterações eletrocardiográficas comumente associadas à cardiopatia chagásica crônica”, mas, surpreendentemente, conclui-se que “uma possível ligação etiológica chagásica entre as patologias cardíacas e digestivas requeriam investigações adicionais”.

Ainda a título de exemplificação das raras circunstâncias em que a abrangência clínica dos autores não foi absoluta, pode-se questionar a inadequada abordagem do diagnóstico diferencial com a coronariopatia obstrutiva. Entretanto, mesmo sem menção específica ao sintoma anginóide (que se sabe acometer pelo menos 20-30% dos cardiopatas chagásicos crônicos) (Marin-Neto *et al.*, 2007) e sem valorizar as alterações eletrocardiográficas compatíveis com necrose miocárdica nesse contexto, acertadamente os autores registram que “esse é o diagnóstico diferencial mais difícil a ser efetuado”.

Essas escassas noções imperfeitas não desmerecem o valor das inúmeras e inequívocas demonstrações da clarividência dos autores naquele artigo, mesmo passado tanto tempo desde sua publicação. Os resultados acumulados de novas pesquisas, aliados a inovações tecnológicas e a armamentários estatísticos elaborados, continuam a sedimentar-se no terreno científico fertilizado. Salvaguardadas as limitações da época, os aspectos clínicos, radiológicos, eletrocardiográficos e patológicos descritos mantêm o seu valor, e ainda se consagram em nossos dias, agora comprovados por modelos matemáticos e números eloqüentes. Se Laranja e colaboradores demonstravam seus resultados de forma meramente descritiva, a verdade essencial do que descreveram hoje se embasa por intervalos de confiança, *p* estatisticamente significativos e modelos matemáticos de risco ou sobrevida, muitas vezes reunindo essas evidências em revisões sistemáticas e metanálises (Mady *et al.*, 1994; Rassi Jr., Rassi & Rassi, 2007; Salles *et al.*, 2003; Rassi Jr. *et al.*, 2006). No entanto, se não conviveram com a época da medicina baseada em evidências – que, temos que reconhecer, às vezes é limitada pela ditadura de números e valores de *p*, em nada podemos desmerecer a importância de suas informações, que apesar de frágeis para os parâmetros vigentes permanecem corretas e nos fazem questionar inclusive a irrestrita confiança por vezes depositada nos atuais modelos de validação científica.

EPIDEMIOLOGIA

Historicamente, a doença de Chagas acometia pacientes restritos a áreas rurais da América Latina, onde as precárias condições habitacionais permitiam amplo contato com o triatomíneo infectado. O recente controle parcial da transmissão vetorial em alguns países da América Latina (Uruguai em 1997, Chile em 1999 e Brasil em 2006), a obrigatoriedade das reações sorológicas no contexto transfusional na década de 80 e as correntes migratórias urbanas e para fora da América Latina mudaram o perfil epidemiológico da doença (Dias, 2007). Um novo conceito de distribuição da doença de Chagas no mundo globalizado se estabeleceu por sua verificação em larga escala nos EUA, inclusive com alguns casos autóctones, gerando a obrigatoriedade do controle transfusional naquele país desde 2006 (Bern *et al.*, 2007), além da disseminação em países da Europa, como a Espanha (Gascon *et al.*, 2007), e mesmo em locais distantes como o Japão (Takeno *et al.*, 1999). Novas e

surpreendentes formas de transmissão, como as ocorridas a partir de transplantes de órgãos (Bern *et al.*, 2007), são descritas em todo o mundo.

No Brasil, mesmo após o controle da transmissão vetorial pelo *Triatoma infestans*, vivemos o que se pode chamar de uma endemia urbana. Áreas antes preservadas como a Amazônia já apresentam casos autóctones (Xavier *et al.*, 2006), e são também consideradas endêmicas. Além disso, números crescentes de surtos por transmissão oral têm ocorrido na Amazônia e no sul do país (Pinto *et al.*, 2008; Tatto *et al.*, 2007). A forma aguda sobrevive nesses casos de transmissão oral, que se apresentam com particularidades, como a gravidade maior associada ao maior inóculo e manifestações menos usuais como o tamponamento cardíaco (Pinto *et al.*, 2008).

CLÍNICA

Impressionante a preciosidade das descrições da fase cardíaca crônica com suas variadas manifestações eletrocardiográficas, radiológicas e clínicas, com bradi e taquiarritmias, morte súbita e insuficiência cardíaca. Apesar de descrita a possibilidade de formação de trombos intracavitários, o acidente vascular encefálico tromboembólico não foi realçado por Laranja e seus colaboradores. Hoje reconhecemos ter essa complicação da doença de Chagas significado extremamente importante, seja pela mortalidade a ela associada ou pela grave limitação funcional imposta aos sobreviventes (Sousa *et al.*, 2008).

Os autores já compreendiam que as diversas alterações eletrocardiográficas se associavam a significados prognósticos distintos. Por exemplo, apesar de o bloqueio de ramo direito ser bastante freqüente e isoladamente benigno, correlacionava-se a desfecho fatal quando associado à fibrose em parede anterior. Da mesma forma, arritmias ventriculares complexas eram comuns em pacientes com insuficiência cardíaca. Com base na evolução das noções já expostas naquele trabalho, hoje conhecemos modelos estatísticos que associam cada uma das alterações eletrocardiográficas da cardiopatia chagásica a um significado prognóstico, traduzido por disfunção miocárdica moderada a grave, permitindo o início do tratamento dos pacientes por ela acometidos, mesmo quando não há a informação mais refinada do ecocardiograma (Sousa *et al.*, 2001). A incorporação desse método, não disponível à época de Laranja, constituiu fundamental recurso para o entendimento da fisiopatologia e para embasar medidas terapêuticas precoces na evolução natural da doença. Foi possível verificar *in vivo* as alterações primeiramente descritas como aspectos patológicos, que tão caracteristicamente assinalam o caráter segmentar inicial da disfunção ventricular na doença de Chagas. De forma intrigante, no trabalho de Laranja e colaboradores não se destacou a lesão mais típica, inapropriadamente chamada de “pseudo-aneurisma” apical.

Em nosso tempo, o ecocardiograma tornou-se indispensável para o diagnóstico diferencial com outras cardiopatias, definindo o tipo de acometimento miocárdico (difuso ou segmentar), o grau de disfunção ventricular sistólica e diastólica, além da presença de complicações como trombos intracavitários e regurgitações valvares associadas (Acquatella, 2007) e, mais recentemente, avaliação do grau de assincronismo intra e interventricular. Deve-se, no entanto, lamentar que, em muitas circunstâncias, a ecocardiografia tenha negligenciado a avaliação da função ventricular direita, concentrando-se quase que exclusivamente no ventrículo esquerdo. Isso explica parcialmente que a relevância do comprometimento daquela câmara tenha sido mais precocemente detectada com o método da angiocardiorrafia nuclear (Marin-Neto & Andrade, 1991) e esclarece o mecanismo da congestão sistêmica assinalada por Laranja e colaboradores em chagásicos com insuficiência cardíaca.

TRATAMENTO

Não houve mudança no tratamento etiológico da doença de Chagas nestes últimos cinquenta anos, e ainda persiste a dúvida sobre os benefícios do benzonidazol na fase crônica da cardiopatia chagásica. Está em andamento grande estudo clínico randomizado, de benzonidazol *versus* placebo (Benefit), envolvendo diversos pesquisadores da América Latina (Marin-Neto *et al.*, 2008).

Os grandes avanços da nossa época são associados ao tratamento da insuficiência cardíaca, estendendo-se empiricamente aos chagásicos os benefícios da terapia tríplice com inibidores da enzima conversora de angiotensina, β -bloqueadores e espironolactona, além do claro benefício do transplante cardíaco (Bochi & Fiorelli, 2001), antes proscrito para a cardiopatia chagásica; também há substanciais recursos para controle de taqui e bradiarritmias, com uso de marca-passos e desfibriladores implantáveis, com ou sem terapia de ressincronização, e possibilidade de ablação de arritmias ventriculares complexas, em casos selecionados. Esperamos com isso reduzir a morbimortalidade desta doença que completa cem anos de descoberta, mas que, infelizmente, permanece negligenciada. É imperativo, sobretudo, manter em foco a noção de acometimento muito predominante em populações de origem humilde e menos abastadas, que hoje se espalham ao redor do mundo em busca de melhores condições de sobrevivência.

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Revisitando os Achados do Centro de Estudos e Profilaxia da Moléstia de Chagas do Instituto Oswaldo Cruz em Bambiú, MG: desafios ainda atuais na compreensão da cardiomiopatia chagásica

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Hoje, sabe-se que a importância médica da tripanossomíase americana precedia a sua descoberta por Carlos Chagas em 1909 (Chagas, 1909), pois foram descobertas múmias apresentando sinais clínicos e material genético do *Trypanosoma cruzi* datadas de 9.000 anos (Araújo *et al.*, 2009). Contudo, o reconhecimento pela comunidade científica e pela sociedade da importância médica e social da doença de Chagas somente foi possível após o trabalho resultante de um esforço coletivo. Esse trabalho foi iniciado por Carlos Chagas, ao descrever o agente etiológico (*Trypanosoma cruzi*), seu vetor, inseto da família Reduviidae, o ciclo do

parasito e as principais características clínicas da nova doença, e encontrou sustentação e validação nos trabalhos desenvolvidos por Emmanuel Dias, Francisco Laranja e colaboradores nas décadas de 40 e 50, que culminaram com a publicação do artigo de revisão por Laranja e colaboradores em 1956.

Chagas descreveu as principais características da fase aguda da tripanossomíase americana (Chagas, 1909, 1910, 1911, 1916), mostrando que esta nova entidade nosológica apresentava um perfil peculiar de sinais clínicos, tais como distúrbio de excitabilidade cardíaca, distúrbios de condução e bloqueio cardíaco completo, delineando, assim, a forma cardíaca da tripanossomíase americana (Chagas, 1911). Nos anos seguintes, Chagas e Villela (1922), utilizando o então recentemente descrito método não invasivo de acesso e registro da atividade elétrica do coração (eletrocardiografia), assim como parâmetros bem descritos para caracterização das alterações cardíacas, descreveram os perfis eletrocardiográficos da fase aguda e crônica em pacientes infectados pelo *T. cruzi*. Contudo, nesse trabalho o reduzido número de pacientes levou a questionamentos sobre a relação entre os achados clínicos e a presença da infecção pelo parasito, assim como sobre a relevância epidemiológica da tripanossomíase americana (Laranja *et al.*, 1956). Os importantes trabalhos de Mazza (1949) e Romaña (1935), desenvolvidos na Argentina, levaram à identificação da fase aguda de modo completo, incluindo o sinal de porta de entrada do parasito pela mucosa ocular, conjuntivite esquizotripanósica, posteriormente denominado sinal de Romaña. Esse sinal clínico levou à identificação da infecção chagásica aguda em 15 países da América Latina no período de 1913 a 1945 (Laranja *et al.*, 1956), mostrando que a infecção pelo *T. cruzi* era amplamente disseminada nesta região. Contudo, inúmeros questionamentos, incluindo os de autoridades da Saúde e membros da Academia de Medicina, sobre a importância médica e epidemiológica da fase crônica da doença permaneceram (Laranja *et al.*, 1956). Foi a partir da criação do Centro de Estudos e Profilaxia da Moléstia de Chagas, posto avançado do Instituto Oswaldo Cruz (IOC) criado em 1943 na cidade de Bambuí, Minas Gerais, coordenado por Emmanuel Dias, que a real situação epidemiológica e a importância social da doença crônica começaram a ser descortinadas, levando à definição da forma cardíaca crônica da doença de Chagas como uma entidade clínico-anatômica distinta.

O Centro de Estudos em Bambuí contava com equipe multidisciplinar, incluindo cardiologista (Francisco Laranja), infra-estrutura e equipamentos para estudos eletrocardiográficos e capacidade de realização de provas sorológicas de Guerreiro-Machado (“calibrado por mais de 250 casos diagnosticados parasitologicamente”). Principalmente, contava com o afimco de pesquisadores dedicados a responder perguntas herdadas de Carlos Chagas, tais como a importância epidemiológica e social da doença de Chagas.

Nos cerca de dez anos de estudos feitos em Bambuí (localidade que na época contava com 26.913 habitantes), foram estudados 235 casos de fase aguda, com acompanhamento eletrocardiográfico, observadas 22 mortes (taxa de mortalidade de 9,4%) devidas a insuficiência cardíaca congestiva, convulsões e infecções associadas, notando-se a maior gravidade e mortalidade em crianças, que em muitos casos apresentavam meningoencefalite (Laranja *et al.*, 1956). Interessante notar que a meningoencefalite é a principal manifestação clínica observada nos casos de infecção pelo *T. cruzi* associada à imunossupressão, como a infecção pelo vírus da imunodeficiência adquirida (HIV), o que levou a Organização Mundial da Saúde (OMS) a considerar a doença de Chagas como uma infecção oportunista na síndrome da imunodeficiência adquirida (Aids) (Vaidian, Weiss & Tanowitz, 2004). Por outro lado, segundo os dados atuais do Ministério da Saúde, com marcante queda em casos agudos por transmissão vetorial após o sucesso do controle do principal vetor no Brasil (Dias, 2007), dos 2.476 casos

agudos notificados 85 foram a óbito, no período 2001-2006, em todas as regiões do território brasileiro (Ministério da Saúde, 2009), com taxa de mortalidade de 3,8%, ainda muito elevada. Em muitos casos, a demora do diagnóstico, e conseqüente tratamento, pode ter contribuído para a alta mortalidade na fase aguda, o que reflete a necessidade de método adequado para o diagnóstico sorológico eficiente e rápido dessa fase da infecção (Coura, 2007).

Como resultado dos estudos realizados em Bambuí, com uso da sorologia e dos exames eletrocardiográficos foi possível a identificação da cardiopatia chagásica, com suas formas oligo e assintomáticas (Prata, 2009). Vários foram os trabalhos publicados a partir desses estudos (Dias, Laranja & Nóbrega, 1945; Dias & Laranja, 1948; Laranja, Dias & Nóbrega, 1948), culminando em 1956 com a revisão intitulada “Chagas disease: a clinical, epidemiologic, and pathologic study” publicada no volume 14, páginas 10.35 a 1.060, da *Circulation*, periódico oficial da American Heart Association, ainda hoje a revista de maior impacto (e maior fator de impacto) na pesquisa em cardiologia.

Na resenha apresentada neste volume por Andrea Silvestre de Sousa e José Antônio Marin-Neto, os diversos aspectos das alterações clínicas, com ênfase na cardiopatia aguda e crônica, foram revistos e contextualizados de forma crítica à luz dos conhecimentos atuais. Assim, nesta resenha, a ênfase recairá sobre alguns aspectos gerais da patologia e, principalmente, os aspectos patogênicos dos achados revistos por Laranja e colaboradores, assim como sua contextualização atual.

No trabalho, Laranja, Dias, Nóbrega e Miranda descrevem as três fases, até aquele momento, do estudo da doença de Chagas: a descoberta por Carlos Chagas; o período de caracterização da fase aguda 1913-1943, com as contribuições de Chagas (1909, 1911, 1916), Vianna (1911) e Torres (1915, 1917), assim como dos médicos argentinos Mazza e Romana; os cerca de dez anos após a criação do Centro de Estudos do IOC em Bambuí, com a confirmação e considerável extensão dos dados originais de Chagas em pacientes crônicos, a caracterização das formas clínicas e estudos epidemiológicos e sorológicos.

Como um dos resultados dos estudos de Bambuí, o emprego de testes sorológicos (reação de Guerreiro-Machado), associado às características clínicas, permitiu a criação de uma base confiável para o diagnóstico da forma crônica cardíaca doença de Chagas (Laranja *et al.*, 1956). De modo interessante, Laranja e seus colaboradores indicavam a necessidade da realização de inquéritos (entomológicos e de diagnóstico humano) que permitissem o real dimensionamento do significado da doença de Chagas no continente americano. Foi somente no período de 1975 a 1980 que o primeiro Inquérito Nacional de Prevalência, com sistematização das metodologias epidemiológica e sorológica, foi realizado no Brasil. Nesse inquérito utilizou-se o método sorológico de hemaglutinação e coleta de sangue em papel de filtro, técnicas mais simples e confiáveis do que a complexa reação de Guerreiro-Machado (Dias & Prata, 2007). O estudo realizado em localidades com mais de 2.500 habitantes revelou uma prevalência global de 4,2% de infecção pelo *T. cruzi*, mostrando que naquele momento cerca de quatro milhões de brasileiros estavam infectados, com taxas muito altas em alguns estados, como Minas Gerais e Rio Grande do Sul (8,8%), Goiás (7,4%), Distrito Federal (6,1%), Sergipe (6%) e Bahia (5,4%). Esse inquérito teve papel fundamental na priorização e no desenho das estratégias de controle da endemia no Brasil, que resultaram no controle do principal vetor da doença de Chagas (*Triatoma infestans*) em 2006 (Dias, 2007). Inquérito sorológico mais recente, em crianças abaixo de 5 anos de idade, revela, ainda de forma preliminar (com análise de quase cem mil amostras), 0,021% de prevalência, havendo positividade em apenas seis estados (CE, PB, AL, BA, MG e RS), o que indica o sucesso

do controle do vetor e a quebra da transmissão vetorial e reforça a necessidade de que a vigilância entomológica seja mantida (Dias & Prata, 2007).

O estudo da fase crônica em 1.340 pacientes, com acompanhamento eletrocardiográfico, mostrou que a infecção e a doença não faziam distinção entre sexos (650 homens e 690 mulheres). Ainda que faltem estudos estatísticos no trabalho de Laranja e colaboradores (mudança nos estudos médicos adotadas somente algumas décadas depois), a análise dos gráficos mostra maior frequência de envolvimento cardíaco em homens nas faixas etárias compreendidas entre 20 e 50 anos e equalização nas faixas etárias acima de 50 anos de idade (Laranja *et al.*, 1956, figuras 7 e 8). De forma interessante, estudos recentes vêm demonstrando que a presença de estrogênio é um fator protetor para cardiopatias (Babiker *et al.*, 2002), incluindo a cardiopatia chagásica (Souza *et al.*, 2001).

Na revisão de Laranja e colaboradores, o *Trypanosoma cruzi* (ainda referido como *Schizotrypanum cruzi*) é apresentado como agente etiológico relacionado às manifestações clínicas, corroborando as observações iniciais de Chagas (1909, 1911), Chagas e Villela (1922), Vianna (1911) e Torres (1917). O encontro de formas amastigotas do *T. cruzi* foi registrado em todos os casos estudados de fase aguda (19 dos 22 óbitos registrados no período), associado à miocardite ativa com presença de infiltrados inflamatórios predominantemente mononucleares.

Somente três décadas depois, as observações originais de Chagas, mostrando distúrbios cardíacos em pacientes cronicamente infectados pelo *T. cruzi*, foram experimentalmente reproduzidas em cães e confirmadas em grande número de pacientes (Laranja, Dias & Pellegrino, 1950; Laranja *et al.*, 1950, 1956). No estudo realizado por Laranja e colaboradores, em todos os 21 casos estudados observou-se aumento do peso cardíaco, com dilatação das cavidades cardíacas. Também nesse estudo, os dados originais de Chagas em cardiopatas crônicos, detectando ninhos de amastigotas em cardiomiócitos e parasitos fagocitados por macrófagos (Chagas, 1916; Chagas & Villela, 1922), foram confirmados em todos os 21 casos com quadro de cardiomiopatia crônica (CCC) estudados, ainda que fosse uma atividade que consumisse muito tempo em observações microscópicas. As alterações histopatológicas no tecido cardíaco de pacientes cronicamente infectados foram bem caracterizadas, mostrando que tais pacientes apresentam infiltrados inflamatórios difusos e focais, com o predomínio de linfócitos, plasmócitos e macrófagos, mesmo que eosinófilos e neutrófilos sejam também encontrados. Além disso, fibrose focal e difusa do miocárdio foi encontrada em todos os casos estudados, variando de um caso para o outro e em um mesmo caso, de uma região do tecido para outra (Laranja *et al.*, 1956). Nesse estudo, foi sugerido que a isquemia do miocárdio é uma das principais causas do desenvolvimento e progressão da doença cardíaca crônica na infecção chagásica. Contudo, nessa revisão os autores não tecem considerações maiores sobre a patogenia da CCC. Cerca de quarenta anos antes, Chagas havia compilado seus estudos histopatológicos, em casos agudos e crônicos humanos e em modelos experimentais, propondo que os mecanismos patogênicos que levam às manifestações cardíacas seriam intenso parasitismo associado à intensa miocardite na fase aguda e persistência do parasito, ainda que para encontrá-lo fosse preciso maior tempo de estudo do material, paralela à inflamação na infecção crônica (Chagas, 1916).

Ainda que o trabalho de Laranja e colaboradores reafirme esses achados, mostrando a coexistência do parasito e da inflamação em todos os pacientes CCC estudados, de modo intrigante, durante as décadas seguintes cientistas eminentes não encontraram o parasito nas lesões cardíacas na maioria de casos crônicos da doença de Chagas. Além disso, os achados de tais cientistas levaram à proposição de que na patogenia da CCC estão envolvidos

eventos auto-imunes (Santos-Buch & Teixeira, 1974; Ribeiro dos Santos & Hudson, 1980; Kierszenbaum, 1985). Essa proposição teve impacto negativo no desenvolvimento de novas quimioterapias visando à eliminação do agente etiológico e no desenvolvimento de vacinas contra a infecção pelo *T. cruzi* (Kierszenbaum, 2005). De fato, somente cerca de oitenta anos após os estudos de Chagas (1916), e mais de trinta anos após o artigo publicado por Laranja e colaboradores (1956), a adoção de métodos imunoistoquímicos e de biologia molecular em tecido cardíaco de pacientes CCC (D'Ávila Reis *et al.*, 1993; Higuchi *et al.*, 1997; Jones *et al.*, 1993; Reis *et al.*, 1997) e os bem desenhados experimentos de transferência de células em modelos experimentais (Tarleton, Zhang & Downs, 1997) levaram cientistas contemporâneos a resgatar a importância do parasito na patogenia das alterações cardíacas na infecção chagásica crônica. Assim, as propostas atualmente mais aceitas indicam que as injúrias cardíacas crônicas em pacientes chagásicos sejam resultado da resposta imune desregulada induzida pela persistência do parasito (Higuchi *et al.*, 2003; Kierszenbaum, 2005).

Nos últimos anos, houve muitas contribuições ao entendimento da fisiopatogenia da miocardite e da cardiomiopatia chagásica crônica (Higuchi *et al.*, 2003; Marin-Neto *et al.*, 2008). Entretanto, não foram desenvolvidas novas abordagens terapêuticas, além das já disponíveis drogas tripanocidas, Benznidazol e Nifurtimox, desenvolvidas na década de 70, e intervenções objetivando o tratamento de sintomas (Marin-Neto *et al.*, 2008; Soeiro & Castro, 2009). Considerando-se que transplante cardíaco é o único tratamento efetivo para milhões de pacientes que já desenvolvem, ou desenvolverão em futuro próximo, a insuficiência cardíaca grave, terapia celular objetivando a recuperação da função cardíaca, ainda restrita a ensaios clínicos, tornou-se uma perspectiva plausível (Soares *et al.*, 2007). Assim, o principal desafio atual é o desenho de tratamentos eficazes para a cardiomiopatia induzida pelo *T. cruzi*, com o desenvolvimento de estratégias que reduzam a inflamação, associada aos danos teciduais (Freitas *et al.*, 2005), sem interferir com o controle do parasitismo (Lannes-Vieira *et al.*, 2003; Marino *et al.*, 2004; Medeiros *et al.*, 2009). Para tal, o resgate do conhecimento gerado pelos trabalhos desenvolvidos no Centro de Estudos do IOC em Bambuí, revisados por Laranja e colaboradores (1956), pode contribuir para trazer para o momento atual as questões levantadas naquela época sobre a origem das alterações patológicas, suas relações com os quadros clínicos e a necessidade de desenvolver drogas tripanocidas e intervenções terapêuticas que melhorem o prognóstico dos pacientes.

Assim, os trabalhos realizados no Centro de Estudos do IOC em Bambuí por Emmanuel Dias, Francisco Laranja e seus colaboradores envolvendo cerca de 2.100 pacientes cronicamente infectados e 280 casos agudos contribuíram enormemente para a confirmação junto à comunidade médica e científica, assim como às autoridades da Saúde, da importância médica e social da doença descrita quase cinquenta anos antes por Chagas (1909). Esse modelo de estudo multidisciplinar, e tudo o que se seguiu a ele, como o tratamento e acompanhamento dos pacientes, realizados ainda hoje pelas equipes médicas que continuaram o exemplo de Dias, Laranja e colaboradores, nos servem de exemplo de como a determinação e a dotação de recursos públicos, com equipamentos de tecnologia de ponta e pessoas altamente qualificadas, munidas de determinação e paixão, podem contribuir para o esclarecimento de uma questão científica e social, dando retorno à sociedade à medida que a instrumenta com o conhecimento para a busca de solução para seus problemas. Por último, fica a lição de que a boa ciência encontra seu lugar no espaço e no tempo, assim como permanece atemporal e servindo de exemplo para gerações futuras, que a redescobrem nesta oportunidade de comemoração e delas podem se apossar de modo a construir ações que mudem o curso dos ainda milhões de indivíduos portadores da infecção chagásica.

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