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A 4-Year Follow-up Study of a Rural Community with Endemic Chagas' Disease*

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The paper reports on a 4-year follow-up study that represents the continuation of a previous cross-sectional study on Chagas' disease carried out in a rural community (Belén) in Venezuela. The earlier study included 1210 persons all over 5 years of age out of a total of 1656 inhabitants and demonstrated a high prevalence of Chagas' infection (47.3 %) and a high rate of Chagas' disease seropositivity among those with chronic myocardial heart disease (84.8 %); heart disease was found in 17.3 % of persons studied. The follow-up study was based on 812 persons and established that in the sample the frequency of Chagas' infection was 16.3 % and that of heart disease 2.2 %. Clinical, electrocardiographic and radiological analyses were made on patients with previous heart disease as well as on new patients. Different evolutive electrocardiographic patterns have been found, including variations ranging from normal to definitively abnormal.

In some Latin American countries Chagas' disease constitutes one of the major clinical and health problems. Heart involvement is a common and severe consequence of this disease, being responsible for invalidism and many deaths in young adults (WHO Study Group on Chagas' Disease, 1960; Romaña, 1961).

Chronic Chagas' heart disease is a variety of inflammatory chronic myocardial disease. Its established form has been repeatedly described from a clinical and pathological point of view (Laranja et al., 1956; Andrade & Andrade, 1955; Bruni Celli et al., 1959; Mignone, 1958; Mijares, 1965; Morales Rojas et al., 1959; Gil Yépez et al., 1962). However, different aspects of the natural history of this condition require further studies (*Bull. Wld Hlth Org.*, 1965).[5]

The purpose of this paper is to report the 4-year results obtained from a longitudinal prospective study being carried on in a Venezuelan rural community (Belén) with high prevalence of Chagas' infection and chronic myocardial disease. The results of the initial examination (cross-sectional study) made in 1961 have already been published (Puigbó et al., 1961).

The objectives of this study are to determine the frequency of heart disease and Chagas' infection in the area, to study the natural history of chronic Chagas' heart disease, to assess the risk among initially seronegative and seropositive groups of developing heart disease, and to establish diagnostic criteria for Chagas' heart disease in its different stages of evolution.

MATERIALS AND METHODS

Out of 1210 subjects initially examined, 812 have been subjected to annual medical examinations, including in each case clinical, electrocardiographic and radiological analyses. The complement-fixation test for the diagnosis of Chagas' infection was

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performed in series among the group initially seronegative. All persons with a positive serological reaction were considered as having suffered from Chagas' infection.

Patients with positive serology and clinical, or electrocardiographic or radiological evidence (or any combination thereof) of myocardial involvement, and in whom the possibilities of another etiology could be safely discarded, were classified as chronic Chagas' heart disease cases.

Patients under 50 years of age with seropositive chronic myocardial heart disease were chosen for special clinical, electrocardiographic and radiological analysis in both the initial cross-sectional study as well as in the follow-up study.

Persons with questionable evidence of heart disease at the first examination were, in estimating incidence, placed with persons in the sample found to have normal hearts.

The serial electrocardiographic changes were classified in two types.

Type 1

This type comprised minor electrocardiographic changes which appeared at one or other of the successive examinations. These changes were not conclusive by themselves for diagnostic classification. Subjects with such electrocardiograms were grouped in a " doubtful " category for subsequent evaluation. The electrocardiograms included in this type showed transient arrhythmias (supraventricular premature beats, unifocal ventricular premature beats, nodal rhythm, wandering pacemaker), slight P-wave alterations, S-wave notching in V_1 and localized, slight and transient alterations of the T wave and ST segment.

Type 2

This type included major electrocardiographic abnormalities. A definitive diagnosis of heart disease was made when such changes appeared in a subject with a previous normal or doubtful electrocardiogram. Included in type 2 were the following:

(1) Intraventricular conduction disturbances, particularly complete right bundle branch block, with or without previous or simultaneous ÂQRSF deviation towards the left and upwards.

(2) Marked, extensive and persistent ventricular repolarization disturbances.

(3) Electrically inactive zones.

(4) Severe arrhythmia, particularly paroxysmal ventricular tachicardia. These were considered as severe arrhythmias because of their clinical implications and their threat to the patient's life, or both. Of this type, the following conditions were observed: atrial fibrillation, ventricular paroxysmal tachycardia and multifocal ventricular extrasystoles.

RESULTS

Serological follow-up

Out of 453 initially seronegative subjects, 74 developed positive serological reaction during the 4-year follow-up interval (4-year incidence of

TABLE 1

4-YEAR INCIDENCE OF CHAGAS' INFECTION AT BELÉN, VENEZUELA, ARRANGED BY AGE AND SEX

Age at initial examination (years)	Both sexes			Males			Females		
	Population at risk [a]	New cases	Rate (%)	Population at risk [a]	New cases	Rate (%)	Population at risk [a]	New cases	Rate (%)
5–14	253	25	9.9	101	11	10.9	152	14	9.2
15-24	80	18	22.5	35	8	22.9	45	10	22.2
25-44	87	22	25.3	37	9	24.3	50	13	26.0
45-64	30	9	30.0	20	4	20.0	10	5	50.0
⩾65	3	—	—	2	—	—	1	—	—
Total	453 [b]	74	16.3	195	32	16.4	258	42	16.3

[a] Persons initially seronegative for Chagas' disease.

[b] In Table 3, 28 persons without heart disease and with serological results that could not be classified have been excluded.

Chagas' infection, 16.3%; Table 1). Hitherto, this serological change has not been associated with the appearance of heart disease.

Cardiovascular follow-up

New cases of heart disease. Out of 812 subjects initially free of heart disease, 18 subjects developed definitive manifestations of heart disease during the 4-year follow-up interval (4-year incidence of heart disease, 2.2%). The incidence rates were 0.7% (3 cases) and 4.2% (15 cases) for seronegative and seropositive groups, respectively (Tables 2 and 3). All new cases were diagnosed as chronic myocardial heart disease, both in the seropositive and in the seronegative group.

In the seropositive group, 15 cases of chronic seropositive myocardial heart disease were found, of which 13 in patients under 50 years of age were analysed. Seven of these cases presented cardiovascular symptoms and 6 were asymptomatic. The distribution of the initial symptoms was: palpitations in 2 cases, syncope in 3 cases, dyspnoea associated with palpitations after great exertion in 1 case and an episode of congestive heart failure

TABLE 2

4-YEAR INCIDENCE OF HEART DISEASE AT BELÉN, VENEZUELA, ARRANGED BY AGE AND SEX

Age at initial examination (years)	Both sexes			Males			Females		
	Population at risk [a]	New cases	Rate (%)	Population at risk [a]	New cases	Rate (%)	Population at risk [a]	New cases	Rate (%)
5–14	360	—	—	151	—	—	209	—	—
15-24	156	3	1.9	73	2	2.7	83	1	1.2
25-44	234	12	5.1	108	4	3.7	126	8	6.3
45-64	57	3	5.3	29	2	6.9	28	1	3.6
⩾65	5	—	—	3	—	—	2	—	—
Total	812	18	2.2	364	8	2.2	448	10	2.2

[a] Persons initially free of heart disease.

TABLE 3

NEW CASES OF HEART DISEASE AMONG INITIALLY SERONEGATIVE AND SEROPOSITIVE GROUPS, AT BELÉN, VENEZUELA

Age at initial examination (years)	Seronegative			Seropositive		
	Population at risk [a]	New cases	Rate (%)	Population at risk [b]	New cases	Rate (%)
5–14	254	—	—	92	—	—
15–24	80	—	—	72	3	4.2
25-44	81	3	3.7	147	9	6.1
45-64	15	—	—	39	3	7.7
⩾65	1	—	—	3	—	—
Total	431 [c]	3	0.7	353 [c]	15	4.2

[a] Persons seronegative and free of heart disease at initial examination.

[b] Persons seropositive and free of heart disease at initial examination.

[c] Excludes 28 persons without heart disease and with serological results that could not be classified.

in connexion with pregnancy and labour in 1 case.

The results of the physical examination were as follows: constant splitting of the second sound always related to complete right bundle branch block in 6 cases (but splitting of the first sound was rarely observed) and extrasystolic arrhythmia in 1 case. The apical impulse was not modified in this group.

Radiological examinations showed that 2 cases featured slight bilateral cardiomegaly predominant in the left ventricle with localized diminution of the cardiac pulsation in 1 of them.

Electrocardiographically, all 13 cases showed type 2 electrical modifications distributed in 3 groups: (1) In 1 case there was the appearance of an electrically inactive zone demonstrated by the diminution in voltage of R in V_4, V_5 and V_6 associated with a ventricular repolarization disturbance. (2) 6 cases had ventricular repolarization disturbances. (3) 6 cases had intraventricular conduction disturbances distributed as follows: 4 cases showed no ÂQRSF deviation (there was the appearance of a complete right bundle branch block in 3 cases and an incomplete right bundle branch block in the fourth); 2 cases had an ÂQRSF deviation towards the left (in one there was the appearance of a complete right bundle branch block with simultaneous ÂQRSF deviation towards the left and in the other an initial ÂQRSF deviation towards the left with the subsequent development of a complete right bundle branch block).

In the seronegative group, 3 new cases of chronic myocardial heart disease, all in patients under 50 years of age, were found and the only evidence of heart disease was a persistent repolarization disturbance.

Evolution of previous chronic Chagas' heart disease cases. Of the 76 cases in patients under 50 years of age followed, 26 did not show any changes and 50 suffered isolated or combined alterations of 3 kinds which were distributed as follows: clinical (in 18 cases), radiological (in 7 cases), and electrocardiographic (in 45 cases).

Specifically, the changes were:

(1) Clinical, including palpitations in 4 cases, extrasystolic arrhythmia in 8 cases, constant splitting of the second sound in 2 cases, paroxysmal ventricular tachycardia in 1 case, abnormal apical pulsation in 1 case, and bilateral congestive heart failure in 2 cases.

(2) Radiological; slight cardiomegaly with predominant enlargement of the left ventricle in 5 cases and moderate to severe in 2 cases. All cases were associated with localized diminution of the cardiac pulsation at the left cardiac border near the apex.

(3) Electrocardiographic; all evolutive electrocardiographic changes observed since the cross-sectional study (1961) up to the present (1965) are shown in Table 4.

Mortality follow-up

Up to the present, 32 deaths have been recorded among the groups under observation; 22 were due to heart failure or were reported as sudden deaths, 4 were due to tuberculosis of all forms, 2 to cancer of all forms and 4 to " other causes ". A total of 10 deaths occurred in the 35–49-years age-group, 7 being due to heart diseases.

DISCUSSION

The study of the specific serology of Chagas' disease during the 4-year period allowed us to demonstrate a high incidence of serology alteration, from negative to positive (Chagas' infection), without the previous appearance of heart disease in any of the subjects suffering this change. This seems to indicate that a period longer than 4 years is necessary for myocardial involvement to occur. The serological change shows a tendency to increase in relation to age, a fact for which no satisfactory explanation has been formulated, although it is possible that a greater immunological response is related to a longer reinfection exposure, as age increases. This correlation was also encountered in the cross-sectional study (Puigbó et al., 1966). The serological changes were not related to sex. The change from negative to positive serology was observed in 2 patients with initial diagnosis of chronic myocardial heart disease. Although it is possible that these 2 cases suffered heart disease from another origin but had also acquired Chagas' infection, it must be noted that the clinical and electrocardiographic evolution was similar to that of chronic seropositive myocardial heart disease. This could suggest that, for immunological reasons not yet clarified, a minority of patients with Chagas' infection did not present initial positive serology. The incidence of heart disease classified as chronic myocardial heart disease was high.

TABLE 4

SERIAL ELECTROCARDIOGRAPHIC CHANGES IN PATIENTS AT BELÉN, VENEZUELA, 1961–65

Electrocardiographic abnormalities at initial examination in 1961 (No. of cases in parentheses)	Evolutive electrocardiographic changes at follow-up examinations (1961-65)									
	RBBB		ÂQRSF development		Arrhythmia		VRD		IEZ [a]	
	A [b]	I [c]	A [b]	I [c]	A [b]	I [c]	A [b]	I [c]	A [b]	I [c]
Intraventricular conduction disturbances present (19)										
Right bundle branch block (RBBB) (17)	—	2	—	1	7	—	11	—	1	—
Left bundle branch block (LBBB) (1)	—	—	—	—	—	—	1	—	—	—
Unclassified intraventricular block (UIB) (1)	—	—	—	—	1	—	1	—	—	—
Intraventricular conduction disturbances absent (24)										
Ventricular repolarization disturbance (VRD) (22)	3	—	1	—	7	—	—	9	1	—
Arrhythmias (2)	—	—	—	—	—	1	1	—	—	—

[a] Inactive electrical zone. [b] Appearance. [c] Increase.

Although the number of cases is small for statistical comparison, the new cases of heart disease showed a tendency to predominate among the seropositive group as compared with the seronegative group (5 times more frequent). The highest proportion of new cases was found in the 25–44 age-group (12 out of 18). There were no cases in patients under the age of 15 years.

The initial symptoms in the group which developed heart disease, as well as in the group with established heart disease, were palpitations and syncope related to rhythm disturbances and not to a complete atrio-ventricular block—a mechanism of syncopal crisis which has also been described in this affection (Laranja et al., 1956; Morales Rojas et al., 1959; Puigbó et al., 1961).

In the initial stages of this particular type of heart disease there was, in general, no evidence of cardiomegaly from physical examination, and the more frequent findings were a constant splitting of the second sound related to right bundle branch block and frequent extrasystoles, spontaneous or provoked by emotion or slight effort. The radiological study provided evidence for the evolution from cases without cardiomegaly to cases with biventricular cardiomegaly, generally slight, with predominant enlargement of the left ventricle. The diminution of the cardiac pulsation previously described (Gil Yépez et al., 1962, 1964; Puigbó et al., 1961, 1966) [1] constitutes an early associated finding. From the electrocardiographic viewpoint, the most significant evolutive factor was the appearance of a right bundle branch block with or without ÂQRSF deviation towards the left and upwards. The tracings showing an established right bundle branch block, isolated or associated with a rhythm disturbance evolved, from the electrocardiographic viewpoint, by the appearance of a ventricular repolarization disturbance, particularly expressed by an increase of the negativity of the T wave from V_2 to V_6.

Two series of electrocardiograms from male patients are given in Fig. 1 and 2.

It is considered that a frequent evolutive pattern is formed by the following elements:

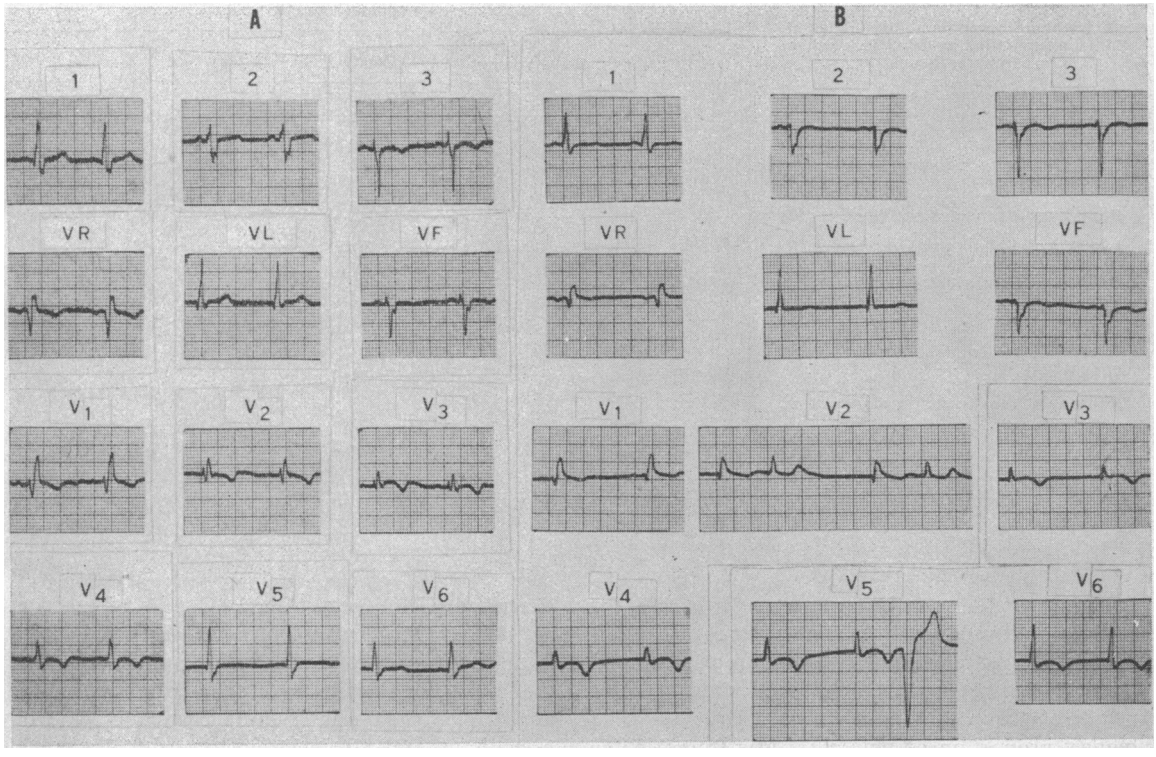
(1) Previous existence or appearance of ÂQRSF deviation towards the left and upwards with or without increase of the voltage, suggestive of left ventricular enlargement (*Bull. Wld Hlth Org.*, 1965; Puigbó et al., 1966).

(2) A qR type of morphology in VL (R higher than 11 mm, with delayed intrinsicoid deflexion).

[1] Also: Pan American Health Organization (1962) *Report of the Advisory Group on research in Chagas' disease* (unpublished document No. Res.1/15).

FIG. 1

ELECTROCARDIOGRAMS FROM J. V., A 42-YEAR-OLD MALE PATIENT WITH A POSITIVE SEROLOGICAL REACTION SPECIFIC FOR CHAGAS' DISEASE



A: Complete right bundle branch block associated with ÂQRSF deviation towards the left; R-wave voltage in VL 11 mm with delayed intrinsicoid deflexion; ventricular repolarization disturbance (22/1/1962).

B: Evolutive pattern in relation with the increase of the ventricular repolarization disorder (negative and symmetric T waves in V_5 and V_6); ventricular extrasystoles (1/6/1965).

These 2 elements can be interpreted as related to the predominance of electrical forces at the basal portions of the left ventricle.

(3) Previous existence or appearance of incomplete or complete right bundle branch block with negative, pointed and symmetrical T waves in V_1 and V_2.

(4) Appearance or increase of a ventricular repolarization disturbance from V_2 to V_6. This disturbance was associated to the absence of transitional complexes and the presence of qRs complexes, representative of epicardial morphology of the left ventricle from V_2 to V_6 (counterclockwise rotation). This type of evolutive pattern was found in 9 out of 11 cases which presented complete right bundle branch block. These combined changes are suggestive of left ventricle enlargement and probably constitute the electrical evidence of anatomical changes at the apex of the left ventricle which frequently occur in chronic Chagas' heart disease (Puigbó et al., 1961, 1966; Pileggi et al., 1961).

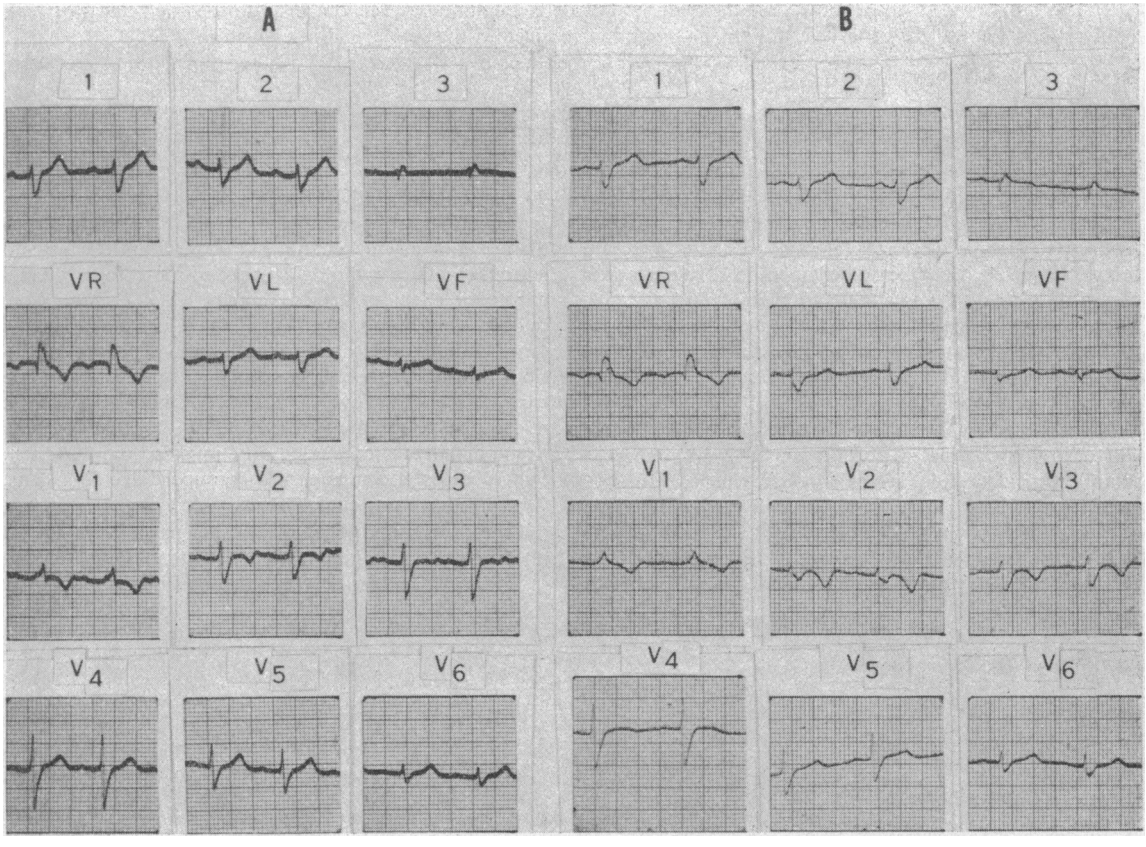
In the group that upon initial examination showed ventricular repolarization disturbances, the evolution was demonstrated by an increase of the repolarization disturbance and, more rarely, by the appearance of a right bundle branch block.

To summarize, in chronic Chagas' heart disease different evolutive electrocardiographic patterns have been determined and are as follows:

(1) Gradual appearance of a complete right bundle branch block. The abrupt change in a tracing, from normal to complete right bundle branch block can be related to the kind of annual

FIG. 2

ELECTROCARDIOGRAMS FROM J. G., AN 8-YEAR-OLD MALE PATIENT WITH POSITIVE SEROLOGICAL REACTION SPECIFIC FOR CHAGAS' DISEASE



A: Complete right bundle branch block associated with ÂQRSF deviation towards the left; ventricular repolarization disturbance (26/9/1961).

B: Increase in the ventricular repolarization disorder (negative and symmetric T waves in V_2 and V_3, low voltage T wave in V_4 and V_5) (25/2/1965).

control employed in this study and by this technique possible intermediate evolutive phases could not be detected.

(2) Appearance or intensification of an ÂQRSF deviation toward the left, with or without other suggestive indications of left ventricular enlargement. This finding may or may not be associated with a right bundle branch block.

(3) Appearance or increase of a ventricular repolarization disturbance from V_2 to V_6 with evidence of counterclockwise rotation in cases with right bundle branch block.

(4) Appearance of a severe cardiac rhythm disturbance generally evidenced by ventricular paroxysmal tachycardia.

(5) Appearance or extension of an electrically inactive zone.

Heart failure and "sudden death" have been the main cause of death in the population under study (68.7%). These causes were responsible for 7 out of 10 deaths in the 35–49 age-group. A high proportion (45.4%) of the mortality due to heart diseases occurred in the 35–49 age-group. The fatality rate among individuals under 50 years of age with chronic seropositive myocardial heart disease was high (7.4% in a 4-year interval).

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RÉSUMÉ

La présente étude longitudinale fait suite à une enquête transversale effectuée antérieurement dans une collectivité rurale (Belén, Venezuela). Cette première enquête, qui avait comporté l'examen de 1210 personnes âgées de plus de 5 ans sur un total de 1656 habitants, montrait une prévalence élevée de la maladie de Chagas (47,3%) et de la cardiopathie qui lui est associée (17,3%), cette dernière étant observée, dans 84,8% des cas chez des patients à sérologie positive.

Le rapport actuel donne les résultats de quatre années d'études longitudinales portant sur 812 personnes et établit l'incidence de la maladie de Chagas (16,3%), attestée par l'apparition d'une sérologie positive, et de la cardiopathie qui l'accompagne (2,2%). Dans le groupe à sérologie positive, 15 cas de cardiopathie ont été dépistés dont 13, survenus chez des sujets âgés de moins de 50 ans, ont été étudiés. Sept de ces cas présentaient des symptômes cardio-vasculaires; chez 6, l'atteinte cardiaque était asymptomatique. Les résultats des investigations cliniques, radiologiques et électrocardiographiques effectuées chez les anciens comme chez les nouveaux malades sont rapportés en détail. On a constaté différents types évolutifs d'électrocardiogramme, depuis les variations du tracé autour de la normale jusqu'aux anomalies caractérisées. Pendant la période d'observation, on a relevé dans le groupe étudié 32 décès, dont 22 attribués à une défaillance cardiaque ou étiquetés « mort subite ». Sur 10 décès survenus dans le groupe d'âge 35-49 ans, 7 étaient dus à une cardiopathie.

De cette enquête, il semble résulter par ailleurs que les altérations cardiaques caractéristiques n'apparaissent qu'après plus de 4 ans d'évolution de la maladie de Chagas.

REFERENCES

Andrade, Z. A. & Andrade, S. G. (1955) *Bol. Fund. Gonçalo Moniz.*, **6**, 1

Bruni Celli, B., Mijares, M. S., Aleman, C., Von Shilling, G. & Berrios, G. (1959) *Arch. Hosp. Vargas.*, **1** (suppl.), p. 61

Bull. Wld Hlth Org., 1965, **33**, 257

Gil Yépez, C., Puigbó, J. J., García Barrios, H. & Nava Rhode, J. R. (1962) *Rev. Soc. venezol. Cardiol.*, **3**, 69

Gil Yépez, C., Puigbó, J. J., Nava Rhode, J. R. & Suárez, J. A. (1964) *Trib. méd. (Santiago)*, **2** (63), p. 1

Laranja, F. S., Dias, E., Nobrega, G. & Miranda, A. (1956) *Circulation*, **14**, 1035

Mignone, C. (1958) *Alguns aspectos da anatomia patologica da cardite chagasica crónica*, Thesis, Faculty of Medicine, São Paulo

Mijares, M. S. (1965) *Arch. Hosp. Vargas.*, **7**, 117

Morales Rojas, G., Hernandez, P. O., Fuenmayor, G., Collet, H. & Gonzalez, R. (1959) *Arch. Hosp. Vargas.*, **1** (suppl.), p. 5

Pileggi, F., Ebaid, M. & Tranchesi, J. (1961) *El vectocardiograma en la miocardiopatía chagásico crónica*, Editorial Interamericana

Puigbó, J. J., Gil Yépez, C. & Nava Rhode, J. R. (1961) *El estudio radiológico de la cardiopatía chagásica crónica.* In: *Symposium sobre enfermedad de Chagas*, Caracas, Hospital Vargas

Puigbó, J. J., Nava Rhode, J. R., García Barrios, H., Suárez, J. A. & Gil Yépez, G. (1966) *Bull. Wld Hlth Org.*, **34**, 655

Romaña, C. (1961) *Bol. Ofic. sanit. panamer.*, **51**, 390

WHO Study Group on Chagas' Disease (1960) *Wld Hlth Org. techn. Rep. Ser.*, **202**