

Long-term control of Chagas disease in Venezuela: effects on serologic findings, electrocardiographic abnormalities, and clinical outcome

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ABSTRACT To evaluate the long-term effects (20 years) of a Chagas control program (CCP) in Venezuela, a prospective serologic evaluation was carried out from 1981 to 1984 on 5771 inhabitants (8%) of Roscio county. This region was selected as a representative area where the national CCP was implemented effectively. Comparison with a serologic survey performed in the same region before the CCP disclosed a reduction in seropositive subjects from 47.8% to 17.1% ($p < .001$), most marked amongst children and teenagers from 29.9% to 1.9%, suggesting that transmission of the disease had diminished. Similar seropositivity changes after the CCP were observed nationwide. Because decreased superinfection would also be expected to occur, we tried to ascertain whether the clinical outcome of seropositive individuals living in Roscio county had improved. The mean age of seropositive subjects between both surveys increased significantly from 34.9 ± 17.3 to 46.7 ± 15.1 years ($p < .001$). Additionally, we examined clinically and obtained electrocardiograms from 775 seropositive subjects. They were classified as asymptomatic (group A, $n = 614$) or as symptomatic, having mild-to-moderate heart symptoms (group B, $n = 99$) or having advanced congestive heart failure (group C, $n = 62$). Their electrocardiograms were compared with those of 923 seronegative subjects collected simultaneously and with published data obtained before the CCP. Comparison of the age-related rates of electrocardiographic abnormalities of seropositive individuals before and after the CCP showed that they did not differ significantly by linear regression analysis, by the Kruskal-Wallis test, or by the normal approximation to the binomial distribution. However, the proportion of symptomatic patients below 50 years of age from series collected before the CCP were significantly higher (more than 50%) than ours after the CCP (12%; $p < .001$). This disparity suggests that future CCP monitoring should include both clinical and electrocardiographic assessment. Five years follow-up (mean 28 ± 18 SD, range 1 to 60 months), showed survival rates at 3 years of $98.4 \pm 0.6\%$ (SE) for group A ($n = 263$), $87.4 \pm 3.8\%$ for group B ($n = 44$), and $37.8 \pm 7.8\%$ for group C ($n = 13$). Although a majority of our seropositive individuals are asymptomatic and had a fair clinical outcome, survival is still poor in those presenting with heart failure. Because effective treatment for the disease is largely unsatisfactory at present, preventive CCPs should be continuously supported.

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ABOUT 20 MILLION PEOPLE living on the American continent who are infected with *Trypanosoma cruzi* are at risk for developing chronic Chagas heart disease.¹ Housing improvement, community education, and use of insecticides against triatomine vectors have been organized in various countries as Chagas control programs (CCPs) to prevent human infection. In Venezuela a CCP began in 1960 and by 1980

involved one of the largest populations covered by such a program,² including Roscio county where the disease is highly endemic. Chronic Chagas heart disease may take 10 to 20 years to develop,¹ but little is known about how a decrease in *Trypanosoma cruzi* transmission and superinfection might change the clinical presentation of the disease. Because as a national electrocardiographic and clinic evaluation of persons living in all areas covered by a CCP would be quite expensive, we have screened serologically a large portion of the Roscio county population since 1981 as a sample of the national CCP and have examined Chagas seropositive individuals to test the hypothesis that two decades of the program might be associated with an improved

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clinical outcome and a decrease in the rates of electrocardiographic abnormalities.

Materials and methods

The data for this cross-sectional case-control study were collected prospectively over 3 years from June 1, 1981, to June 1, 1984, at the Centro de Investigaciones "Jose Francisco Torrealba" (CIT) in San Juan de los Morros in the north central plain of Venezuela. San Juan with four other surrounding *municipios* constitutes Roscio county. The serologic diagnosis of Chagas disease (titers of 1:8 or more) was performed at the CIT laboratory and at the Division de Endemias Rurales (DER) by one or more of the following techniques: complement fixation,³ immunofluorescence,⁴ and in most by indirect hemagglutination.⁵ The sources of our subjects were as follows: all persons attending the County Blood Bank (43%), persons attending the CIT outpatient clinic either spontaneously (19%) or referred (17%), and persons seen in rural and school surveys (21%). In 3 years, 8277 subjects from the Roscio and surrounding counties were screened. Serum results from 247 subjects (3%) were discarded for various laboratory technical reasons, leaving 8030 subjects whose age, sex, and place of origin were stored in a data file. Of these, 5771 were Roscio county inhabitants. Chagas seropositivity was present in 986 subjects, of whom 775 were examined and constitute our clinical population. The remaining 211 subjects could not be contacted a second time for examination.

Clinical and electrocardiographic classification. A detailed history of the seropositive subjects was taken. They were given a physical examination and functionally classified according to the New York Heart Association (NYHA) criteria. Each was examined at least once by conventional 12 lead ECG and chest radiography. The electrocardiographic criteria for abnormality according to the NYHA⁶ and the electrocardiographic classification of normal, borderline, and abnormal for the study of Chagas disease of Maguire et al.⁷ were used. Radiologic cardiomegaly was graded as mild, moderate, and severe (cardiothoracic ratio 0.50 to 0.53, 0.53 to 0.55, and over 0.55 respectively). Interpretation of ECGs and chest films was performed independently by two of the authors without knowledge of the subject's clinical history. The clinical grouping of each subject was determined by a panel of at least three of the authors as follows:

Asymptomatic (group A). The asymptomatic population consisted of apparently healthy individuals having normal, borderline, or abnormal ECGs. Cardiomegaly was absent in all subjects

below 50 years of age or was only mild in a few older subjects.

Symptomatic (groups B and C). The symptomatic consisted of patients showing abnormal or borderline ECGs. They were divided in two groups. Those in NYHA classes I or II (group B) included subjects with either arrhythmia-related symptoms, five or more extrasystoles per minute, or embolic episode as first symptom. Radiologic heart size ranged from normal to severe cardiomegaly. Those in NYHA classes III or IV (group C) had overt congestive heart failure. Most had severe cardiomegaly and various arrhythmias.

Control (group D). The control data consisted of a number of prospectively consecutive electrocardiograms obtained from seronegative Roscio county inhabitants.

Statistical analysis. Data are expressed as mean \pm SD. Nominal data were analyzed by chi-square statistics in contingency tables. The population mean age from Chagas seropositive epidemiologic studies performed before the CCP was calculated by group statistics and compared with our results by Student's unpaired t test. Survival rates were estimated by actuarial analysis⁸ as well as their standard errors and 95% confidence intervals.⁹

Our age-related rates of electrocardiographic abnormalities were compared with those reported in epidemiologic studies before the CCP. These studies¹⁰⁻¹² were selected because inclusion of the raw data allowed us to perform statistical comparisons. Since the relationship between cohort age in years and their respective rates of electrocardiographic abnormalities were not normally distributed, values were corrected by angular transformation¹³ for the linear regression analysis. We compared intercepts *a* and slopes *b* for significant differences between our results and those observed before the CCP. Differences between the proportions of electrocardiographic abnormalities and the respective number of persons at each age cohort were tested by the normal approximation to the binomial distribution.¹⁴ Since the electrocardiograms were obtained from different populations under different treatment, we also performed Kruskal-Wallis statistics¹⁵; *p* < .05 was considered significant.

Results

Roscio county Chagas control program. Although sporadic, pilot dieldrin spraying against the vectors *Rhodnius prolixus* and *Triatoma maculata* began in 1953, and it was not until 1961 that DER began a methodical CCP. In the 1961-1963 serologic survey (table 1),

TABLE 1
Chagas serologic surveys before and after CCP

Age (yr)	Before (1961-63)			After (1981-84)		
	Population ^A screened (%)	Serology + % ^B		Population ^A screened (%)	Serology + % ^B	
		n	%		n	%
0-9	1.5	192	18.2	2.2	445	0.2
10-19	3.7	318	29.9	5.5	983	1.9
20-29	2.5	166	53.6	13.7	1877	6.5
30-39	3.4	170	65.9	12.8	1029	21.1
40-49	3.9	134	76.1	12.2	630	35.4
>50	4.9	175	68.0	11.6	807	50.1
All	2.9	1155	47.8	8.0	5771	17.1

^AEstimated from Roscio county population census performed in 1961 (40,309 inhabitants) and in 1981 (71,756 inhabitants).

^B+ = positive. Before vs after: chi-square = 37.3, *p* < .001.

Chagas seropositivity (complement fixation) was found in 552 of 1155 persons (47.8%; mean age 34.9 ± 17.3 years). From 1961 to 1980 the Roscio county CCP has examined a mean of 2477 ± 1160 houses per year (range 1031 to 5927). The mean percentage of houses containing vectors was $6.4 \pm 4.8\%$, with a range of 18.1% (initial) to 1.7% (latest). The mean number of captured triatomine per year that were examined for presence of *Trypanosoma cruzi* in feces was 1290 ± 1104 (range 251 to 3763). The mean percentage of vectors containing the parasite was $0.41 \pm 0.53\%$, ranging from 2.1 to 0 over the last 3 years.

From 1981 to 1984, a total of 8.0% of the Roscio county population was screened (table 1). Chagas seropositivity was found in 986 of 5771 persons (17.1%; mean age 46.7 ± 15.1 years). For children and teenagers born during the CCP, the percentage of seropositivity was less than 2%. Compared with the high serologic rates obtained in the 1961–1963 study, our results showed a strikingly significant statistical difference at all age cohorts (chi-square = 37.1) and in mean age ($p < .001$ in both). We found no significant difference in seropositivity between sexes by age cohort (chi-square = 1.89, $p > .8$).

Clinical findings. Of the 775 seropositive subjects (mean age 47.3 ± 14.5 years), 614 were in group A (79%; mean age 45.1 ± 14.2 , range 18 to 90 years), 99 were in group B (13%; mean age 53.9 ± 12.0 , range 26 to 79 years), and 62 were in group C (8%; mean age 58.7 ± 12.3 , range 32 to 81 years). There were significant differences in the mean ages between groups. Group A subjects were significantly younger than those from either group B or C, whereas group C patients were older than those from group B ($p < .001$ in all cases). Clinical grouping showed a distribution according to age: below 50 years there were 438 subjects, of whom only 51 (12%) were symptomatic, whereas at 50 or more years there were 337 subjects, of whom 111 (32%) were symptomatic, a highly significant difference (chi-square = 51.0, $p < .001$). We found no subjects with acute Chagas disease. The mean age of 211 unexamined persons was 46.1 ± 14.5 years, not significantly different from that of the examined group ($p > .2$).

Electrocardiographic findings (table 2)

Group A. The ECG was normal in 61% of the subjects, borderline in 12%, and abnormal in 27%. The percentage of subjects having normal ECGs was age related, ranging from 91% in teenagers to 18% in the seventh decade. Right bundle branch block and left anterior fascicular block were the only abnormalities significantly higher than in group D ($p < .001$).

Groups B and C. The ECG was abnormal in 89% of the patients and borderline in the rest. Percentages of nearly all ECG abnormalities were significantly higher than those presented by either group A or D. Arrhythmias were present in all. Right bundle branch block, left anterior fascicular block, and unifocal ventricular premature contractions were the most frequent findings.

Group D. Among 923 seronegative subjects (mean age 40.5 ± 15.5 , range 6 to 85 years), the ECG was normal in 76%, borderline in 10%, and abnormal in 14%.

The rates of abnormal ECGs were significantly higher (table 3) in seropositive (39%) than in seronegative subjects (14%; chi-square = 145, $p < .001$).

Mortality. A five year follow-up to May 30, 1986 (mean 28 ± 18 months, range 1 to 60) included 596 group A subjects (97%) and 159 group B and C patients (99%). We could not locate for follow-up 18 subjects in group A and one each in groups B and C. Fifty-three subjects died, 30 men and 23 women (mean age 57.4 ± 10.5 , range 32 to 80 years). The events leading to death were congestive heart failure in 19 patients, sudden death in 19, cerebrovascular accident in four, can-

TABLE 2

Electrocardiographic findings in Chagas seropositive (A, BC) and seronegative (D) groups

Findings	A		BC		D	
	n	%	n	%	n	%
	614	100	161	100	923	100
RBBB	66 ^A	9.3	64 ^A	39.8	12	1.3
IRBBB	9	1.5	3	1.9	9	1.0
LAFB	66 ^A	9.3	62 ^A	38.6	36	3.9
LBBB	2	0.3	4 ^A	2.5	8	0.9
AV 1-2	10	1.6	23 ^A	14.3	10	1.1
AV 3	0	0.0	4 ^A	2.5	1	0.1
AF	0	0.0	30 ^A	18.6	6	0.7
VPC	20	3.3	121 ^A	75.2	40	4.3
ARRHYT	34	5.5	161 ^A	100.0	58	6.3
Q	7	1.1	39 ^A	24.2	16	1.7
ST	15	2.4	19 ^A	11.8	17	1.8
T	69	11.2	49 ^A	30.4	84	9.1
LAE	9	1.5	38 ^A	23.6	21	2.3
LVH	23	3.7	23 ^A	24.3	29	3.1

RBBB = right bundle branch block; IRBBB = incomplete right bundle branch block; LAFB = left anterior fascicular block; LBBB = left bundle branch block; AV 1-2-3 = atrioventricular first, second, and third degree block; AF = atrial fibrillation; VPC = unifocal and multifocal ventricular premature complexes; ARRHYT = all arrhythmias; Q = abnormal Q waves; ST = abnormal ST elevation and depression; T = flat and inverted T waves; LAE = left atrial enlargement; LVH = left ventricular enlargement.

^A $p < .001$, A vs D, or BC vs D, by chi-square analysis.

TABLE 3
Percentages of abnormal electrocardiograms by age

Age (yr)	Chagas serology			
	Positive ^A		Negative ^A	
	n	%	n	%
0-9	—	—	4	0.0
10-19	11	9.1	61	3.3
20-29	76	13.2	187	1.6
30-39	163	20.9	214	4.7
40-49	188	35.6	186	12.4
>50	337	57.3	271	32.1
All	775	39.2	923	13.5

^AChi-square = 145; $p < .001$.

cer in four, liver cirrhosis in one, and unknown in six. Deaths occurred in 32 group C subjects, in 13 group B, and in eight group A. The 3 year percent survival rates and cumulative SEs, were $98.4 \pm 0.6\%$ for group A, $87.4 \pm 3.8\%$ for group B, and $37.8 \pm 7.8\%$ for group C. There were significant statistical differences in survival between the three groups at 3 and 5 years follow-up ($p < .01$ in all, except for A vs B at 5 years, $p < .05$) (figure 1).

Discussion

The aim of a CCP is to curtail disease transmission to uninfected subjects and to prevent superinfections. The two-decade control program in Roscio county has sharply diminished transmission of Chagas disease as demonstrated by the low seropositivity rates in children and teenagers and by the absence of recognizable cases of acute disease. It has also prevented superinfections and delayed the appearance of clinical cardiac damage to mid-late instead of early adulthood.

Although we compared two serologic surveys performed 20 years apart, the decrease in seropositivity rates are so striking (table 1) that they almost certainly cannot be explained by differences in test sensitivity. On the contrary, improvements of the sensitivity in the serology technique used¹⁶ would yield an increased number of seropositive subjects. Similar decreases have occurred in other areas of the country,¹⁷⁻¹⁹ as in Brazil,²⁰⁻²³ Chile,²⁴ and Argentina.²⁵ However, there are other possible reasons that cannot be excluded, such as migrational changes of seropositive and seronegative subjects in and out of Roscio county, the attrition of those previously sick before our study began, and sampling differences between both surveys. We also found a significant difference in the mean age of our seropositive population; in the initial survey of our area as well as from other populations studied before the

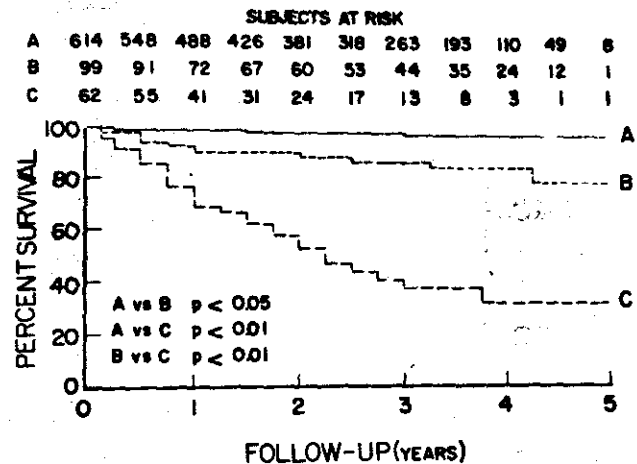


FIGURE 1. Survival of 775 Chagas seropositive subjects according to clinical groups. A denotes asymptomatic, B and C moderately and severely symptomatic subjects, respectively. Survival rates among the three groups were significantly different at 3 years ($p < .01$) and at 5 years (shown in figure). The 95% confidence limits at 5 year follow-up were 97.0% to 98.7% for group A, 72.3% to 86.2% for group B, and 14.2% to 48.8% for group C.

CCP, the mean ages tend to cluster in the third decade (34.9 ± 17.3 , 32.0 ± 17.5 ,¹⁰ 31.1 ± 15.9 ,¹¹ and 39.3 ± 17.2 ¹²) while our group mean age after the CCP was 46.7 ± 15.1 years ($p < .001$ vs all).

A decrease in superinfections should also have occurred in our seropositive subjects, presumably leading to less severe forms of the disease. To address this issue, we used both electrocardiographic and clinical evaluation. The age-related rates of electrocardiographic abnormalities from three studies performed in Chagas seropositive subjects before the CCP, two available from Venezuela^{10, 11} and one from Argentina,¹² were compared with those obtained by us after the CCP (figure 2). Linear regression analysis disclosed no significant differences in slopes ($p > .25$) or intercepts ($p > .5$). Furthermore, no differences before and after the CCP were found by the Kruskal-Wallis test ($p > .9$), nor by the normal approximation to the binomial distribution in the proportions of electrocardiographic abnormalities by age. The exceptions were two out of 15 comparisons, which may be explained by the fact that the electrocardiographic criteria used in the four studies were not strictly identical. Seronegative subjects had significantly lower rates of electrocardiographic abnormalities than seropositive subjects before¹⁰⁻¹² and after the CCP (table 3) (intercepts $p < .001$).

This lack of electrocardiographic improvement in seropositive persons after the CCP contrasts sharply with the beneficial clinical course we observed. Clin-

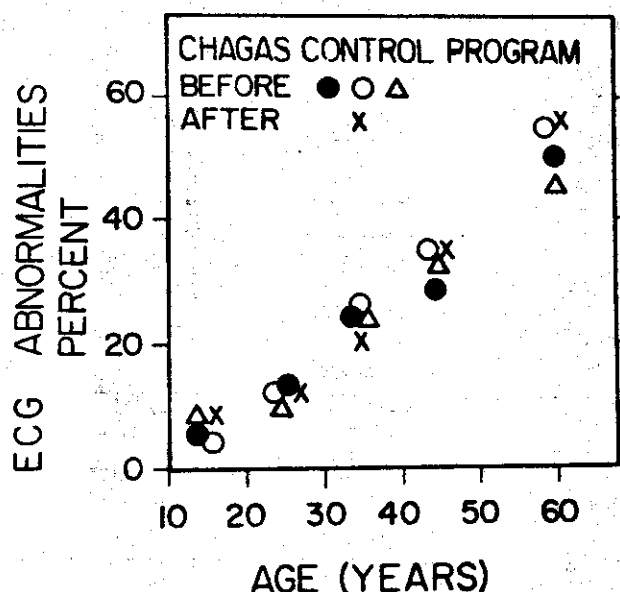


FIGURE 2. Percent of electrocardiographic abnormalities in Chagas seropositive subjects obtained from epidemiologic studies performed before and after the CCP. Closed circles denote results from Pifano *et al.*,¹⁰ open circles from Puigbo *et al.*,¹¹ and open triangles from Rosenbaum and Cerisola.¹² Our results are denoted as X. No significant differences by linear regression analysis (corrected by angular transformation) were found in slopes ($p > .25$) or intercepts ($p > .5$). Chagas seronegative subjects (not shown in the figure) had significantly lower rates of electrocardiographic abnormalities than seropositive subjects (intercepts $p < .001$).

ical studies performed before the CCP consistently stressed that chronic Chagas heart disease afflicted mainly young and middle-aged individuals. For example, in our country, Puigbo *et al.*¹¹ noticed in subjects under 50 years of age that 63 out of 95 (66%) were symptomatic. Likewise, Torrealba examined 291 subjects from and around Roscio county²⁶ between 1934 and 1958: one-third suffered from acute Chagas disease, and 31 out of 41 patients showing heart failure were below 50 years of age. In Brazil, Laranja *et al.*²⁷ noticed in their classic study that 82% of patients with chronic Chagas heart disease were between 11 and 50 years of age. In contrast to these studies, only 12% of our subjects below 50 years of age were symptomatic, significantly lower than in the population of Puigbo *et al.*¹¹ (chi-square = 136, $p < .001$). If we had relied only on electrocardiographic analysis we would not have detected this improved clinical outcome.

The improved outcome of subjects with chronic Chagas heart disease was reflected nationally in our annual health statistics.²⁸ Available estimated age at death throughout years 1966 to 1969 was 55.9 ± 15.5 years (range 55.3 to 56.9) and increased to 63.1 ± 13.0 years (range 61.3 to 64.2) throughout years 1979 to 1982 ($p < .001$). It was noteworthy that in our popu-

lation mean age at death was well over 50 years (57.4).

Our study suffered from the difficulty involved in contacting persons living in remote rural areas for follow-up. We could not examine 211 seropositive persons initially detected (21%). Nevertheless, since their mean age was not different from that of our study population ($p > .2$), we presumed that their age-related clinical and electrocardiographic abnormalities were similarly distributed as in the examined group. The reduction in the number of young and middle-aged patients we found could be fictitious if the unexamined group was composed mostly of symptomatic Chagas subjects. It was reassuring that even if all the 144 unexamined persons below age 50 years were symptomatic, the increase to 33.5% of the total would still be significantly lower than before the CCP (chi-square = 35.9, $p < .001$). We would have liked to examine the same subjects screened 20 years ago but were unable to identify them.

Finally, an important source of our population was obtained through the County Blood Bank, which led to self-referred or physician-referred potential sampling bias. However, it should be pointed out that we found no significant differences between the age-related percent seropositivity rates of our population with those obtained randomly throughout the country by DER in Chagas endemic areas, either before or after the CCP (chi-square = 0.73, $p > .9$; and 3.05, $p > .6$, respectively, table 4). Furthermore, the absence of significant differences in our rates of age-related electrocardiographic abnormalities with surveys performed in our country and in Argentina 20 years ago (figure 2) supports the view that our study groups represent a valid sample from a chronic Chagas population. It is possible that our potential sampling bias was mostly diminished by the large amount of the population screened (8%). We could not compare our results with a "control" area not covered by the CCP, since the program was applied nationwide. Future studies are necessary to corroborate our results.

In conclusion, the Chagas control program decreased disease transmission sharply but did not diminish the appearance of electrocardiographic abnormalities in seropositive persons. At present clinical manifestations of chronic Chagas heart disease appear in patients of more advanced age than before. Although the pathogenesis of the disease is still poorly understood, diminished infection and prevention of superinfection²⁹ may in part explain the observed improved outcome of middle-aged Chagas seropositive individuals. Other changes, such as control of other parasitic diseases, improvement in nutrition, and hab-

TABLE 4

Chagas serologic surveys performed in endemic areas of the country (excluding Roscio county) before and after CCP^a

Age (yr)	Before (1958-68)			After (1980-84)		
	Persons examined n	Serology +		Persons examined n	Serology +	
		n	% ^b		n	% ^c
0-9	1145	239	20.8	14294	167	1.2
10-19	3475	981	28.2	13977	286	2.1
20-29	1694	822	48.5	5287	707	13.4
30-39	1506	933	61.9	3425	943	27.5
40-49	1217	790	64.9	2586	1009	39.0
>50	1060	684	64.5	4017	1893	48.4
All	10097	4449	44.1	43586	5005	11.5

^aPerformed by DER (Division Endemias Rurales, Ministry of Health of Venezuela).^{17, 19}^bCompared with Roscio county survey (table 1), chi-square = 0.73, $p > .9$.^cAs in B, chi-square = 3.05, $p > .6$.

itat may also have produced favorable influences. Because Roscio county represents a sample from the nationwide CCP, it is possible that the changes reported here should be more widespread. Continuing support for Chagas control programs are therefore justified.

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