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PUBLICAÇÃO IEA Nº. 153
Agôsto — 1967

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Caixa Postal 11049 (Pinheiros)
CIDADE UNIVERSITÁRIA "ARMANDO DE SALLES OLIVEIRA"
SÃO PAULO — BRASIL

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+ Publicado em Acta Endocrinológica - 53(1966) 162-176

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RESUMO

Os autores procuram estudar o comportamento da Tireóide, na moléstia de Chagas, através da análise de provas funcionais realizadas em três grupos de pacientes portadores da moléstia em sua forma crônica. Verificaram não haver correlação entre a moléstia de Chagas e o bócio e não haver diferenças significantes entre os valôres médios do PBI nos chagásicos e nos contrôles. Entretanto, a dispersão dos resultados no grupo dos chagásicos foi muito maior do que entre os testemunhos; a diferença entre as respectivas variânças foi significativa. A variação diária do PBI no grupo dos chagásicos foi significantemente maior do que no grupo de referência. Os achados sugerem a existência, nesta moléstia, de uma alteração dos mecanismos envolvidos na manutenção da homeostase tireoidiana, que poderia correr por conta das lesões neuronais características da moléstia, que envolveriam etapas nervosas dos circuitos de homeostase.

RÉSUMÉ

Le comportement de la glande thyroide a été étudié, à partir d'essais fonctionnels, sur trois groupes de malades atteints de la maladie de Chagas sous sa forme chronique. Les auteurs ont vérifié qu'il n'existe pas de relation entre goître et maladie de Chagas. Ils ont pu également constater que les valeurs moyennes du PBI du groupe témoin ne diffèrent pas significativement de celles du groupes de Chagas. Il y a, malgré cela, une dispersion des valeurs individuelles beaucoup plus importante dans le groupe chagasien; la différence entre les varian

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ces est statistiquement significative. La variation quotidienne du PBI dans le groupe chagasien est significativement plus importante que la variation dans le groupe de référence. Ces résultats conduisent à penser à l'éxistance, dans cette maladie, d'une altération du mécanisme de régulation de l'homéostasie thyroidienne qui pourrait être causée par les lésions neuronales caractéristiques de la maladie de Chagas chronique qui seraient capables d'affecter les liaisons neuronales des circuits homéostatiques.

ACTA ENDOCRINOLOGICA
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By

D. A. Lomonaco, H. L. Oliveira, J. Kieffer and R. R. Pieroni

ABSTRACT

The problem of thyroid dysfunction in Chagas' disease is discussed on the basis of the functional study of three series of patients with the chronic form of the disease. There was no significant association between Chagas' disease and goiter. No significant difference was found between the average plasma PBI in the groups of patients and that of the control groups. However, the values in the Chagas groups showed a much wider dispersion than those of the non Chagas controls; the difference between the corresponding variances was statistically significant. A loss of efficiency of the mechanisms concerned with the homeostasis of circulating thyroid hormone seems to occur in chronic Chagas' disease. This is interpreted as a possible result of the nervous lesion characteristic of the disease, which might involve neuronal links of homeostatic circuits responsible for the release of TSH.

The problem of thyroid involvement in Chagas' disease is as old as the earliest descriptions of the clinical picture of infection by *Trypanosoma cruzi* (*Chagas* 1910, 1911 *a,b,* 1912, 1916). Hypothyroidism was believed to be one aspect of that picture; the main features leading to such conclusion were the goiter and the oedema frequently observed by the pioneer students of the disease.

This work was supported in part by an agreement between the Ministry of Health of Brazil (D. N. E. Ru.) and the Department of Health and Welfare of the State of São Paulo.

Later investigations showed that the generalized oedema which very often accompanies the acute stage of the disease, mainly in children, did not present the characteristics of myxoedema (*Mazza* 1939; *Talice* 1940; *Dias et al.* 1945; *Laranja et al.* 1948; *Rassi et al.* 1958). On the other hand, the presence of goiter in many patients with Chagas' disease was later explained as a result of overlapping of independent goitrous and chagasic endemic areas (*Baeta Vianna* 1931; *Romaña* 1935; *Lobo Leite* 1939). The histological picture of thyroid glands from patients with Chagas' disease has been shown to be comparable to those observed in European endemic goiter (*Penna de Azevedo* 1933, 1936).

The study of thyroid function in patients with Chagas' disease has not been carried out until recently. In 1962 we presented a preliminary analysis of our data (*Kieffer et al.* 1962). In the same year *Lobo et al.* (1962) published their observations, based on thyroid radioiodine uptake and determination of the plasma protein bound iodine (PBI); they concluded that no abnormality could be demonstrated. This conclusion is confirmed in the present work, as far as the average indices for each group of patients is concerned. However, the scatter of the data is abnormal, suggesting the existence of a peculiar defect in the homeostatic mechanisms concerned with the regulation of thyroid function.

MATERIAL AND METHODS

The subjects included in this study were submitted to a clinical examination, for the detection of any signs or symptoms of thyroid dysfunction, and in addition some of the following laboratory procedures were undertaken: determination of the plasma protein iodine, 24-hour thyroid radioiodine uptake and thyroidal function stimulation and depression tests. The diagnosis of Chagas' disease, irrespective of the presence of any clinical manifestation, was based on a positive Machado-Guerreiro complement fixation reactio...

The subjects studied were divided into the following 3 groups, corresponding to the successive steps of the investigation

Group I. (a) 60 patients, admitted to the University Hospital of Ribeirão Prêto for different reasons, who gave a positive Machado-Guerreiro reaction;

(b) 40 normal controls (hospital physicians, students, nurses and technicians), all with a negative Machado-Guerreiro reaction.

Every subject in this group was submitted to clinical examination and to a plasma PBI determination.

Group II. (a) 101 subjects from the urban and rural population of the village of Cassia dos Coqueiros and its surroundings, all with a positive Machado-Guerreiro reaction;

(b) 49 subjects from the same population who gave a negative Machado-Guerreiro reaction.

There was no significant difference between sub-groups (a) and (b) as far as age,

sex, nutrition, occupation and general health conditions were concerned. Subgroup (b) is therefore an adequate control for the sub-group (a). The same could not »a priori« be said of group I; in this respect, the conclusions drawn from the comparison of sub-groups I (a) and I (b) needed corroboration by a new series of data such as those given by group II.

In this group every subject was submitted to clinical examination, plasma PBI determination and the measurement of thyroid radioiodine uptake. In selected cases the thyroid function stimulation or depression tests were also performed.

Group III. (a) 13 patients admitted to the Hospital who had a positive Machado-Guerreiro reaction;

(b) 10 normal controls (Hospital physicians and nurses), all with a negative Machado-Guerreiro reaction.

Daily determination of plasma PBI in fasting blood samples was carried out in each subject of this group for periods of 8 to 25 consecutive days.

Machado-Guerreiro's complement fixation reaction. This reaction was performed in all subjects in accordance with the quantitative technique of *Freitas & Almeida* (1949). It is a very sensitive (positive in over 95 % of patients with proved Chagas' disease) and highly specific test (no false positive result in large series of normal subjects and patients with a variety of diseases other than Chagas' disease) (*Freitas* 1952, 1961).

The iodoproteinaemia (PBI) was determined by the method of *Barker et al.* (1951) with the modifications of *Ubatuba & Hallal* (1957).

The test of radioiodine uptake by the thyroid gland was performed in accordance with the usual techniques and within the norms recommended by the I. A. A. E. 131-Iodine was used for the test. Tracer doses varied between 30 and 50 μc. The percentual fraction taken up by the gland was measured 24 hours after the administration. All counting times were sufficiently long to obtain a number of net counts with an error not langer than 2 %.

Thyroid hormone stimulation test with thyrotrophin. After previous determination of thyroid uptake and PBI, thyrotrophic hormone (TSH) was administered subcutaneously in two does of 5 USP units with a 24 hours interval. Thyroid uptake was measured 24, 48 and 72 hours after the second TSH injection; PBI determinations were repeated every 24 hours until 96–120 hours. At the end of 24 hours, responses of +45 % to +100 % for thyroid uptake and of +70 % for plasma PBI were obtained in normal subjects.

Thyroid hormone suppression test with triiodothyronine (T_3). Following a determination of the thyroid uptake, 100 μg of triiodothyronine (T_3) were given daily for 10 days. On the 11th day a 24-hour thyroid uptake test was repeated.

RESULTS

Group I. Plasma PBI was chosen as the parameter of the thyroid function. The results and their distribution, mean values, standard deviations and variances are shown in Fig. 1.

The mean values for each of the two sub-groups (patients with Chagas' disease and normal controls) are not significantly different. In the chagasic

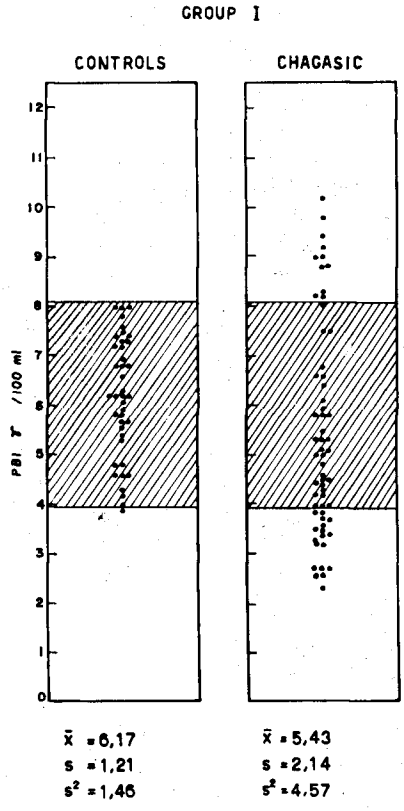

Fig. 1.

Plasma PBI values in normal controls and in patients with Chagas' disease (group I). The difference between their respective mean values (6.17 and 5.43) is not statistically significant; that between their variances (1.46 and 4.57) is significant at the level of 5 % (F-test).

sub-group, however, the individual data are abnormally scattered, above as well as below the limits of 95 % normality. There is an incidence of 28.3 % of results below the lower limit and of 18.9 % results above the upper limit; i. e. a total of 46.6 %, which is a value much greater than the 5 % expected if the chagasic group had the same distribution as the normal. The variances were 1.46 in the normal and 4.57 in the chagasic sub-group; the difference (F-test) *is significant* at the level of 5 %.

The clinical examination, however, did not show in sub-group I (a) any sign of thyroid dysfunction, despite the frequency of PBI values lower than 3 μg and higher than 9 μg, values clearly outside the normal range. However, none of the patients presented a degree of hypoproteinaemia which

could explain the low values, nor was there any iodine contamination to explain the high values.

Group II. The values found for PBI and the characteristics of their distribution are shown in Fig. 2. The mean values corresponding respectively to sub-groups II (a) and II (b) are practically the same (6.26 and 6.11), but their variances are clearly different (2.85 and 1.40); this difference is significant at the level of 5 % by the F test.

A wider range of variation than in the control sub-group is also apparent in the chagasic subjects when the values for thyroid ^{131}I-uptake are considered (Fig. 3). However, the difference between the respective variances is not significant at the probability level of 5 %.

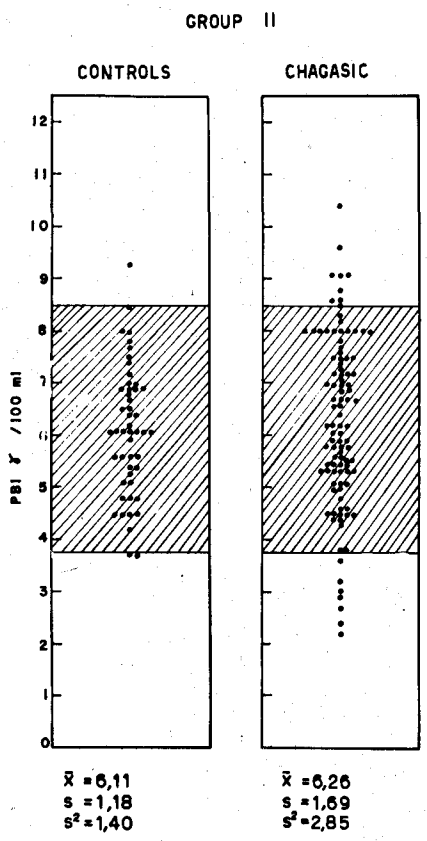

Fig. 2.

Plasma PBI values of group II. The difference between their respective mean values (6.11 and 6.26) is not statistically significant; that between their variances (1.40 and 2.85) is significant at the level of 5 % (F-test).

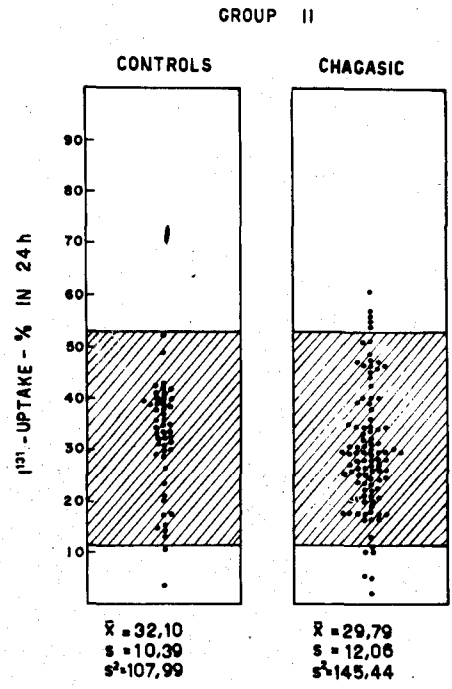

Fig. 3.

Thyroid ^{131}I-uptake in normal controls and chagasic patients of group II. A wider range of variation is apparent among chagasic subjects, but the difference between the variances is not significant.

10 subjects from sub-group II (a) and 5 from sub-group II (b) were submitted to the TSH stimulation test. Instead of causal selection, patients were chosen among those whose ^{131}I-uptake and PBI values had been normal or low. The results are found in Tables 1 and 2. The response to stimulation was within the normal range.

In 5 subjects from sub-group II (a) a depression test with T_3 was performed. We intentionally selected those whose ^{131}I-uptake was higher than the upper limit of normality. The results are shown in Table 3. All subjects showed normal values, with a sharp fall of thyroid ^{131}I-uptake values after depression.

Enlargement of the thyroid gland, mostly slight in degree, was observed in 31.7 % of the chagasic and 28.6 % of the non chagasic subjects. The figures do not lend support to the idea of any causal relation between Chagas' disease and the presence of goiter.

Group III. The study of this group was planned to test the possibility of an abnormal individual variation of PBI as an explanation for the wide dispersion of the values in the chagasic group. The results are shown in Tables 4 and 5.

Table 1.
TSH stimulation test in chagasic subjects from Group II.

Patients	^{131}I uptake (%)			PBI (μg/100 ml)					
	Before	24 hour after TSH	48 hour after TSH	Before	24 hour after TSH	48 hour after TSH	72 hour after TSH	96 hour after TSH	120 hour after TSH
L. A. L.	20.5	71.0	85.0	2.7	7.2	11.7	8.5	–	-
S. S. M.	11.4	64.0	65.5	2.4	5.3	12.5	13.3	14.7	–
J. M. C.	19.4	50.0	–	2.9	4.3	8.0	13.3	–	–
B. C. G.	2.3	62.0	–	3.0	7.7	8.0	–	–	–
A. M.	23.4	65.5	59.0	4.6	9.4	15.8	13.4	–	–
M. F.	–	–	–	2.5	8.1	6.3	7.0	6.7	–
A. F. Q.	–	–	–	2.1	6.6	11.5	7.4	9.4	8.6
H. D. M.	–	–	–	2.6	4.0	7.5	14.5	12.8	8.0
M. M.	–	–	–	4.5	7.8	9.3	9.2	7.5	–
J. D. S.	–	–	–	8.0	10.4	11.4	9.8	10.1	10.3

Table 2.
TSH stimulation test in control subjects from Group II.

Patients	^{131}I uptake (%)			PBI (μg/100 ml)					
	Before	24 hour after TSH	48 hour after TSH	Before	24 hour after TSH	48 hour after TSH	72 hour after TSH	96 hour after TSH	120 hour after TSH
R. C. A.	38.0	81.5	–	8.0	8.0	14.4	–	–	–
R. A.	32.2	86.0	–	7.7	7.4	12.0	–	–	–
M. R. S.	13.5	54.0	56.0	6.7	8.6	9.6	15.6	–	–
P. M. P.	15.0	65.5	57.0	6.9	10.2	12.5	10.9	11.5	9.8
L. V.	–	–	–	4.5	5.6	8.1	5.7	4.7	–

Table 3.
Thyroid hormone depression test with T_3 in chagasic subjects from Group II.

Patients	^{131}I uptake % in 24 hours	
	Before	After T_3
J. B. S.	51.0	9.0
J. V. M.	51.0	11.0
J. C.	55.0	2.6
H. L.	57.0	8.0
L. R. S.	46.5	3.3

In order to verify the methodological variation, repeated determinations were performed in four different sera. The results are found in Table 6. The maximum variation was 2.2 μg/100 ml serum. This range absorbs most of the daily variations found in the control sub-group III (b), as shown in Table 5. In contrast, the variations observed in the patients with Chagas' disease (Table 4) widely exceed those expected from mere methodological fluctuations.

For a comparative study of sub-groups III (a) and III (b) the test of the sequence of the individual variance was chosen. Using this test, one would expect 12 runs to rule out any significance in the difference between the two sub-groups. The occurrence of only 6 runs is very significant (Fig. 4).

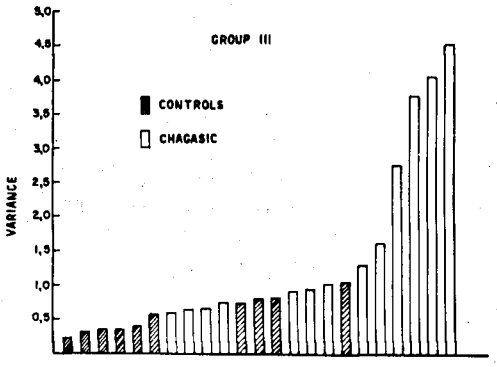

Fig. 4.
Variances of plasma PBI in patients with Chagas' disease and control subjects. Each column corresponds to one subject.

Table 4.
Daily variation of PBI in chagasic patients (Group III).

Patients	PBI μg/100 ml in consecutive days											
	1	2	3	4	5	6	7	8	9	10	11	12
A. R. S.	7.0	6.1	10.1	8.6	6.2	8.3	8.3	9.4	10.0	6.4	6.7	8.0
E. F. M.	12.5	5.8	6.8	10.4	9.7	10.0	6.1	6.1	10.9	7.8	5.8	5.7
J. H. S.	7.3	7.3	7.7	7.7	9.6	5.8	7.3	7.3	8.0	7.2	8.0	5.5
R. P. O.	6.1	6.4	6.4	6.7	6.4	6.3	9.0	6.2	8.3	5.4	6.0	4.5
A. P. S.	8.0	7.5	5.5	6.8	7.4	8.0	6.8	7.1	6.8	7.3	7.8	8.2
M. V. F.	3.8	3.4	6.1	3.1	3.8	3.6	4.4	5.8	3.1	4.4	3.4	2.9
B. R.	3.3	6.2	4.0	4.9	4.6	4.4	5.1	4.2	6.1	4.8	4.7	4.5
A. A. M.	4.8	7.6	8.4	7.9	8.7	8.4	7.0	7.4	6.5	7.6	6.5	7.8
B. B. N.	6.0	9.5	4.5	2.8	4.2	2.8	4.0	4.3	4.8	7.8	5.7	7.0
M. S.	9.7	10.1	7.6	8.0	4.8	8.7	5.5	7.0	10.3	8.9	10.2	10.3
I. R. J.	6.8	8.2	6.7	7.2	8.1	6.5	6.9	5.8	6.0	5.8	6.0	5.7
J. S. R.	5.3	6.1	6.0	7.0	7.9	5.6	5.6	5.0	6.7	5.3	5.8	5.0
J. O. C.	5.6	6.8	6.7	5.8	4.6	5.3	5.8	6.8	7.1	5.2	7.2	7.0

Table 4 (continued).
Daily variation of PBI in chagasic patients (Group III).

Patients	PBI μg/100 ml in consecutive days												
	13	14	15	16	17	18	19	20	21	22	23	24	25
A. R. S.	10.0	7.1	4.9	9.5	6.0	5.8	4.0	4.0	5.2				
E. F. M.	6.8	6.8	6.4	11.2	6.4	8.2	6.4	7.1					
J. H. S.	8.0												
R. P. O.	5.9	6.3	6.3	6.3	6.3	6.0							
A. P. S.	6.8	7.9	8.6	7.5	6.5	8.2	6.9	7.2	6.5	6.5	7.3	7.3	5.2
M. V. F.	4.1	4.1	2.7	3.1	3.8	4.1	3.1	3.8	3.5				
B. R.	4.2	5.5	3.8	6.0	4.6	6.0	5.8	4.3	4.8				
A. A. M.	7.4	5.3											
B. B. N.	5.2	6.1	6.9	5.2	6.7	5.8	6.1						
M. S.	10.6	8.8	10.4	8.8	11.6	11.8	12.6	11.4	10.9				
I. R. J.	6.4	6.1	7.2	6.4	6.1	6.3	3.1	3.1					
J. S. R.	6.9	6.2	5.7	5.6	5.4	6.6	5.0	3.1	5.8				
J. O. C.	5.6	6.7	6.3	5.7	5.4								

Table 5.
Daily variations of PBI in control subjects (Group III).

Subjects	PBI μg/100 ml in consecutive days											
	1	2	3	4	5	6	7	8	9	10	11	12
D. A. L.	7.8	6.8	7.8	7.5	7.5	8.6	7.8	7.5	8.3	8.0		
R. F.	5.8	5.1	6.5	7.6	6.2	5.4	5.8	7.3	7.0	6.9		
M. A. J.	5.9	4.9	5.4	5.2	4.4	3.6	4.4	4.4	4.2	6.1	4.0	4.7
H. R.	6.9	6.9	5.9	5.6	6.6	6.3	7.2	6.3	7.6	5.9		
D. M.	5.7	6.0	6.0	5.7	6.3	6.7	7.0	4.4	6.7	4.4		
J. F. F.	7.2	8.6	7.2	8.7	8.0	8.7	7.8	5.6	6.4	7.3		
J. C. B.	8.0	8.3	6.8	–	6.7	6.5	5.8	7.0	6.1	–		
I. F.	8.0	8.0	7.8	8.0	6.8	8.5	8.1	8.7	8.8	–		
C. G.	5.3	4.8	5.6	6.0	4.4	5.6	5.6	6.4	6.0	5.3		
D. R.	7.3	7.0	8.0	6.3	7.4	7.6	6.5	7.3	7.8	8.0		

Table 6.
Repeated dosages of PBI in dfferent sera.

Serum	PBI μg/100 ml										
	1	2	3	4	5	6	7	8	9	10	11
A	9.7	9.0	9.5	9.7	10.0	9.8	9.8				
B	4.9	5.9	5.5	4.8	5.6	5.0	5.2	4.8	5.2		
C	7.0	8.0	6.5	6.3	6.7	6.7	7.0	7.1	6.3	5.8	8.0
D	4.8	5.6	6.2	5.4	5.3	6.0	6.3	5.0			

DISCUSSION

The analysis of the first part of the results shows a considerable and significant dispersion of the plasma PBI values in patients with chronic Chagas' disease (group I (a)) as compared with a group of normal controls; there is a great frequency of figures higher and lower than the variation limits of 95 % normality. Nevertheless, clinical examination failed to reveal any deviation from euthyroidism. This was very peculiar, since in a significant number of cases the figures obtained were, by the usual criteria, diagnostic

of either hyperthyroidism or hypothyroidism. That this could be a feature of the chronic stage of Chagas' disease was an intriguing possibility and stimulating proposition.

All the data were obtained from a series of hospitalized patients, for which it was difficult to establish an adequate control group. To obviate this, a new study of the problem was carried out in an isolated community with a high prevalence of Chagas' disease, where chagasic and non-chagasic (control) subjects belong to the same social classes and are subjected to the same environmental factors and living conditions. The choice fell on the inhabitants of Cassia dos Coqueiros, a small town in the State of São Paulo, situated in the same endemic area of Ribeirão Prêto. It is an old highly endemic spot, where intensive prophylactic measures have been undertaken in the last 7 years by the Department of Preventive Medicine of the Medical School of Ribeirão Prêto. As a consequence the transmission of the disease is under control and its chagasic population (known through previous repeated surveys) presents almost exclusively the chronic form of the disease.

The results concerning group II confirmed, among the members of such a community, the findings of group I.

Another fact that emerged from the results obtained in Cassia dos Coqueiros was the absence of any causal relation either between goitre and Chagas' disease or between goitre and the dispersion of the PBI values.

The clinical euthyroidal character of both sub-groups II (a) and II (b) was corroborated by the results of the pharmacological tests.

The values of ^{131}I-uptake in the chagasic sub-group were not significantly different from the control. Nevertheless there was a tendency to a greater dispersion, which in a larger sample might probably be significant.

In order to get a better understanding of the existence of large PBI variations without any detectable symptoms of thyroid disfunction, the daily individual PBI variations were studied. The results showed that chagasic subjects had indeed daily variations with a significantly wider scatter than those of the controls. Thus, the variations found for these controls can be attributed in a large measure to methodologic fluctuations; this agrees with the prevalent concept in the literature, i. e. that the PBI is normally a very steady biological constant.

We believe that the data of this last group are of considerable importance in the interpretation of the findings of the daily PBI, with values higher and lower than the normal variation limits, we can foresee the probability of obtaining, in isolated blood samples from a populational group, PBI figures with a distribution analogous to that observed in chagasic patients of groups I and II.

Although both the number of patients studied in group III and the time during which they have been followed are insufficient to establish this, it is

other groups. On account of the extreme variability of the

possible that the plasma PBI fluctuations obtained in chagasic patients, are due to cyclic fluctuations.

The maximal PBI variations must occur within a sufficiently short time interval, so that no clinical manifestations can arise from the variations in the plasma hormone level. This would explain the constant absence of thyroid signs related to PBI disturbances and the clinical euthyroidism, which is maintained by an average PBI level comparable to that seen in the control groups.

On the other hand, stimulation and depression tests carried out on the chagasic patients of group II showed, within the limits of validity of these tests, that the glandular tissue of these patients behave in the same way as that in the normals.

How can we interpret these results and how are they to be explained in the light of present knowledge on the thyroid function and the pathogenesis of Chagas' disease? The key to any attempt to formulate a hypothesis is the fundamental character of the chronic Chagas' disease, and responsible for the impressive variety of functional abnormalities already described. These includes the secretory function of salivary and sweat glands (*Vieira* 1963, 1964); the motor activity and coordination of the oesophagus (*Godoy & Haddad* 1961; *Vieira* 1962; *Haddad & Godoy* 1963; *Vieira & Godoy* 1963), of the stomach (*Vieira & Godoy* 1964), of the colon (*Vieira et al.* 1964), of the bronchi (*Godoy* 1963), the cardiac rate (*Godoy* 1962); and the glucose tolerance curves (*Reis et al.* 1960; *Reis* 1963). A common denominator for all these dysfunctions seems to be a loss of efficiency or different kinds of regulatory mechanisms.

Homeostatic circuits can indeed be directly interfered with by the basic lesion characteristic of the pathology of chronic Chagas' disease. Such lesions cause destruction of neurones, and thus the significant diminution of the number of nervous cells in every organ affected by the disease, as quantitatively shown chiefly by Köberle and his collegues (*Köberle 1959*, 1961 *a, b*; *Köberle et al.* 1961; *Schwartzburd & Köberle* 1959; *Penha & Köberle* 1959; *Alcântara* 1961; *Jardim* 1962) in the autonomous plexuses of hollow digestive viscera, in the heart, in bronchi, in the spinal cord, in the cerebellum. *Köberle* (personal communication) has also found, at a qualitative level, a decrease in the number of neurones in hypothalamic nuclei of rats with experimental Chagas' disease.

It seems particularly reasonable to assume that such a pathology could interfere with the finest regulatory mechanisms depending on hypothalamic relays. One of these might be the TSH-releasing function, resulting in a lowered efficiency of the homeostasis of the circulating thyroid hormone. A delay in putting on the TSH-releasing mechanism, as a response to decreasing concentration of the hormone, would explain the abnormal downward oscilla-

tion of PBI; the release, when it occurs, of the TSH stored during a longer interval, would account for the opposite abnormal shift of PBI values.

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Received on March 30th, 1966.