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NECROTIZING ARTERITIS IN MEGAESOPHAGUS

HISTOPATHOLOGY OF NINETY-ONE BIOPSIES TAKEN FROM THE CARDIA

Thales de BRITO [1] and Edmundo VASCONCELOS [2]

SUMMARY

A study of ninety-one biopsies of cardia in patients with megaesophagus is reported. Histopathology has shown the following:

1 — Plexuses destruction, sometimes with neuromata formation. Chronic inflammatory process has been seen around and inside the destructed structure.

2 — Chronic and subacute interstitial myositis, with formation of the so-called "Entzündungstrasse" (Koeberle) which sometimes goes down to the destructed plexuses.

3 — Focal myositis, sometimes with granulomata formation.

4 — Necrotizing arteritis, with partial or total medial destruction of the arterioles nearby the plexus or located beneath the serosa. The inflammatory process around the vessels is made up mostly of hystiocytes, lymphocytes and a few eosinophiles. It seemed to us that we were dealing with an arteritis probably of the allergic type.

5 — The histopathological process seemed to be progressive, different portions of the esophagus and stomach being affected at different times. The older lesions were located at the cardia.

6 — In one case, leishmanial forms were seen inside a smooth muscle fiber.

7 — Epidemiological and pathological data seem really to point out chronic Chagas' disease as one of the etiopathogenetic factors in megaesophagus in Brazil. A similarity between chronic Chagas' myocarditis and myositis seen in megaesophagus is presented. The allergic factor, which seems to be fundamental in the chronic myocarditis also appears in megaesophagus chiefly through the necrotizing arteritis.

8 — Our findings are in accordance with those described by Fonseca showing that megaesophagus and megacolon are only one manifestation of a more general process, affecting the gastrointestinal tract as a whole.

INTRODUCTION

Studying ninety-one biopsies of the cardia in patients with megaesophagus we had the opportunity to see, besides the lesions already described by the early [1, 11, 45] investigators and more recently by KOEBERLE & col.[21, 23, 25], a necrotizing arteritis. The lesion was similar to the one sometimes seen in hipersensitivity and so far as we know has not been described in megaesophagus.

It is the purpose of this paper to present the morphological description of the above mentioned findings and to suggest a pathogenetic hypothesis regarding megaesophagus in Brazil, which seems to be closely related

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to chronic Chagas' disease [21, 22, 23, 24, 25, 42]. Acquired megacolon apparently has a similar pathogenesis. This paper does not deal with congenital megacolon [5], which is a completely different problem.

MATERIAL AND METHODS

Ninety-one biopsies performed in patients with megaesophagus and operated upon according to the technique of HELLER modified by VASCONCELOS, have been included in paraffin according to the usual methods, after either 10% formalin or Bouin's fluid fixation. Sections were stained routinely with hematoxylin and eosin (H.E.). When necessary, Weigert-van Giesen, PAS-hematoxylin, Masson's trichromic and Mallory's phosphotungstic hematoxylin were also performed. In thirty-two cases three level cuts through the block were obtained to study more carefully the extension of the lesion or the plexuses destruction.

Most of our material is made up of surgical biopsies of the cardia. However, according to the modification of the operatory technique proposed by VASCONCELOS, a small portion of the stomach musculature is also taken out, and, at least in some cases, we had the opportunity of comparing the lesions seen in oesophagus with the ones of the superior third of the stomach. We have also compared the findings in megaesophagus with seven biopsies of megacolon, the morphological picture being essentially the same [9, 10, 18, 30, 39, 45].

Three oesophagectomies were also performed, and in these cases fragments were taken from different levels of the organ.

RESULTS

The first alterations to be discussed are the ones in the plexuses, lesions already seen by the different workers on the subject of megaesophagus [1, 11, 12, 13, 21, 23, 25, 45] and acquired megacolon [9, 10, 39]. In our material we attached little importance to the degenerative neuronal process, a finding which, according to our point of view, can be seen with variable intensity in routine examination of surgical specimens without any accompanying physio-pathological alteration. However, in four of our cases it was striking and worthy of consideration; the fact that in three of them focal areas of total neuronal destruction, with secondary local inflammatory process were seen is also worth mentioning.

Most of the cases have shown, even after three level cuts through the block, a complete neuronal disappearance; in their place there were remnants of Schwann's cells and an inflammatory infiltrate made up of lymphocytes, monocytes and a variable number of eosinophiles. Sometimes, the Schawann's cells appeared proliferated, showing an irregular limit in relation to surrounding tissues, a pattern suggesting the one seen in amputation neuroma (fig. 4). The capillaries close to the plexuses were dilated, containing either red cells or mononuclear cells and eosinophiles. Similar blood vessel changes can be seen in the surrounding connective tissue, the cellular infiltrate being perivascular. Inflammatory infiltrate can also be seen surrounding the small nerve trunks near the serosa.

In more advanced phases there is beginning sclerosis of the plexuses, small connective tissue bands being seen penetrating them. In eight cases we could compare the oesophageal plexuses with the ones of the stomach: a total preservation of them was seen in three cases; the other five have shown early lesions, characterized by inflammatory infiltrate surrounding nervous cells with picnotic nuclei (fig. 5) going up to complete neuronal disappearance. When examination of all the oesophagus was possible, we have found that the oldest lesions were located at the cardia. The lesions became less and less conspicuous as the proximal end of the organ was approached, suggesting that we are really dealing with a progressive disease which affects different portions of the oesophagus and stomach at different intervals of time.

The other finding deserving comment is an interstitial myositis, seen in 52 of the 91 cases (fig. 1). It is focal and made up of an infiltrate of lymphocytes and hystiocytes, a predominance of the last cell type being the rule. The hystiocytes appear as a cell a little larger that the lymphocyte, with nuclei

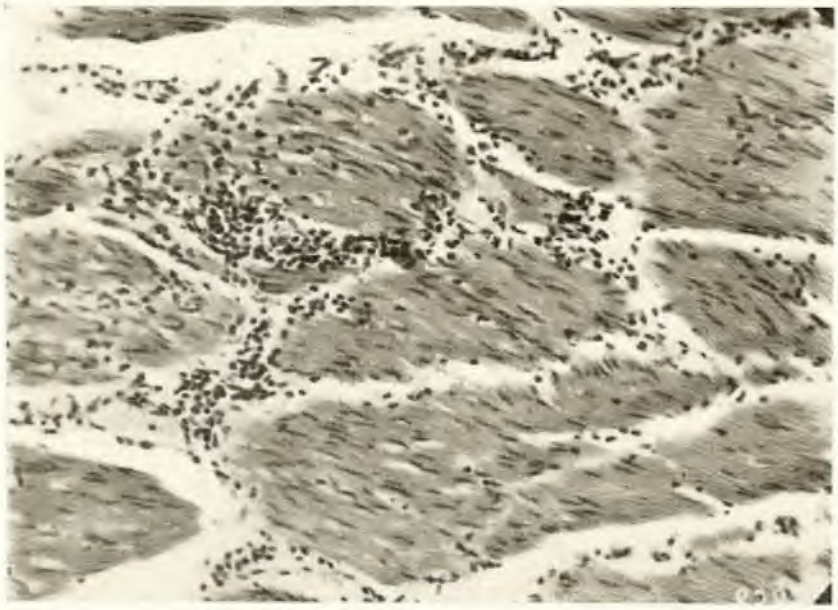

Fig. 1 — (Biopsy MAD 8793) — Chronic inespecific intersticial myositis. Stain: H.E. 300 ×

Fig 2 — (Biopsy MAD 3105) — Chronic interstitial myositis with granuloma formation. Stain: H.E. 300 ×

Fig. 3 — (Biopsy MAD 6319) — Chronic interstitial inflammatory process with granuloma formation. The disposition around an arteriole (periarteritis) is well seen.
Stain: PAS and hematoxylin. 300 ×

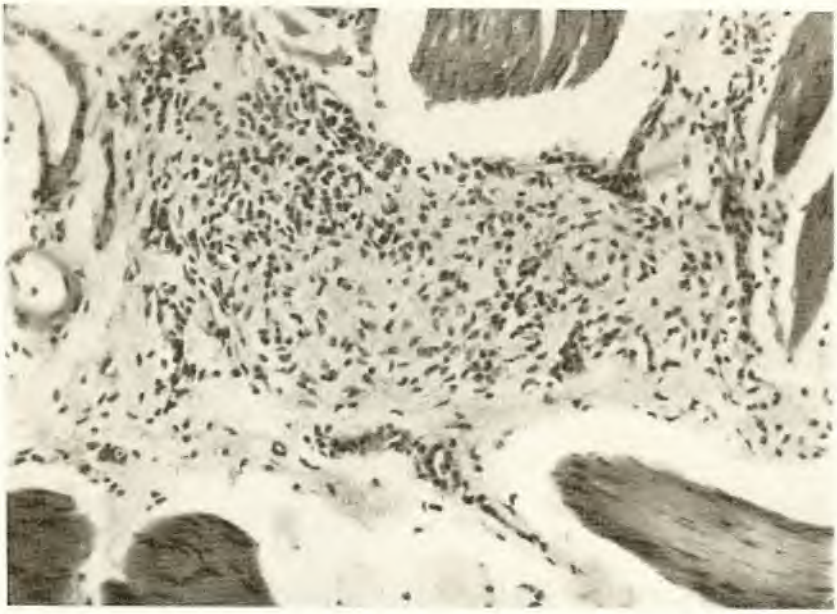

Fig. 4 — (Biopsy 9025) — Plexus showing complete neuronal disappearance and secondary Schwann's cell proliferation, giving the appearance of an amputation neuroma. The inflammatory process, made up mostly of round cells, is also well seen.
Stain: H.E. 300 ×

showing a delicate chromatin network; the cytoplasm is generally basophilic and not prominent. Eosinophiles were also seen. In 12 of the 91 cases, granuloma appeared as groups of hystiocytes surrounded by a peripheral ring of lymphocytes, giant cells either of foreign body or of the Langhams type, being occasionally seen (fig. 2 and 3).

These areas of focal myositis are located around smooth muscular fibers which sometimes show conspicuous alterations represented either by a diffuse hyalinization or by a granular acidophilic aspect of the cytoplasm. This finding is very similar to the one seen in muscle fibers of mice experimentally infected with *Trypanosoma cruzi* by COLLIER & col.[7].

The focal myositis has as sequel small areas of interstitial fibrosis with atrophic smooth muscle fibers in its center. Worth mentioning is the fact that the intensity of the inflammatory process is variable from case to case and even in the same case according to the level cut.

Closely related to the myositis are the so-called "Entzündungstrassen" [21, 23, 25] which are represented by an interstitial inflammatory infiltrate which sometimes surrounds the plexuses. This infiltrate is similar to the one seen focally round damaged muscle fibers, the predominance of the hystiocyte being the rule, granulomatous formations sometimes being observed (fig. 3). However, the tendency of the infiltrate to surround small vessels was striking. The capillaries showed endothelial tumefaction, with partial or total lumen occlusion. The arterioles showed the infiltrate surrounding them (periarteritis) and sometimes invading focally the media. The same disposition could also be seen around small veins giving rise to periphlebites.

Quantitative variation of the infiltrate according to the area and block level were also seen. The "Entzündungstrassen" were seen in 45 cases. Apparently, they can also give rise to patchy irregular areas of fibrosis of the interstitium. Some cases were completely static, an interstitial fibrosis without inflammation was seen, obliterating also the plexuses.

In one case we have seen leishmanial forms inside a smooth muscle fiber (fig. 9), a finding previously described by KOEBERLE [21, 23, 25]. When the parasites are intact no infiltrate is seen around the fiber. However, the leishmaniae inside the smooth muscle fiber can appear also as small individual round corpuscles, few in number, disposed according to the major diameter of the fiber. This disposition has already been described by ROCHA LIMA [43]. We have seen corpuscles with this particular morphology in some fibers. However, we have never been sure if we were dealing with parasites or small fragments of cytoplasm and nuclei.

In 9 of the ninety-one cases, lesions affecting segments of arterioles nearby the plexuses and beneath the serosa were observed. The earlier phase of the lesion is characterized by endothelial tumefaction with or without picnosis of the nuclei of the endothelial cells. PAS positive areas can be seen beneath the endothelium, affecting, focally, the internal portion of the media (fig. 6). The full blown process is characterized by an increase of the PAS positive areas affecting now practically the whole media, with partial or total elastic layer destruction. The PAS positive areas are markedly acidophilic, appearing homogeneously by eosin (fig. 7). Mallory's phosphotungstic hematoxylin and van Gieson stain these areas in yellow. In the evolutive phases of the lesion, a peripheral inflammatory infiltrate disposed as a ring around the affected vessel can be seen (fig. 8). The infiltrate is made up chiefly by hystiocytes, sometimes elongated. A few eosinophiles are also seen.

As we can see, this necrotizing arteritis is morphologically similar to the one described in diseases with a background of hypersensitivity. It is different from the periarteritis above described which probably represents a secondary involvement of the arteriole by the interstitial inflammatory infiltrate. Sometimes we have seen this secondary involvement focally, deep in the media, which shows local tintorial modifications similar to the ones described in necrotizing arteritis.

The necrotizing arteritis in our opinion, is the consequence of a primary aggression

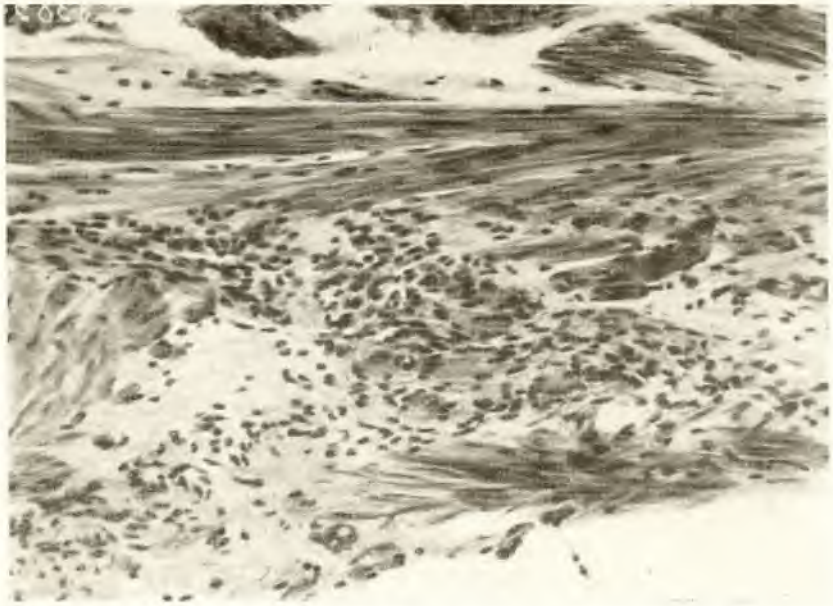

Fig. 5 — (Biopsy MAD 9025) — Plexus of the stomach showing beginning neuronal destruction through inflammatory process.
Stain: H.E. 300 ×

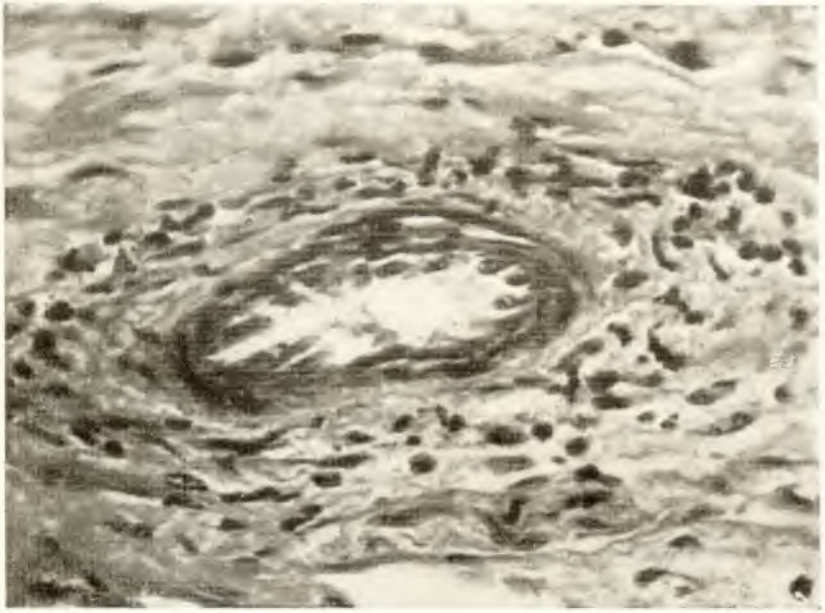

Fig. 6 — (Biopsy MAD 9046) — Arteriole showing nuclear picnosis at the intima and beginning necrosis of the arterial wall. Inflammatory process at the periphery of the vessel.
Stain: PAS and hematoxylin 620 ×

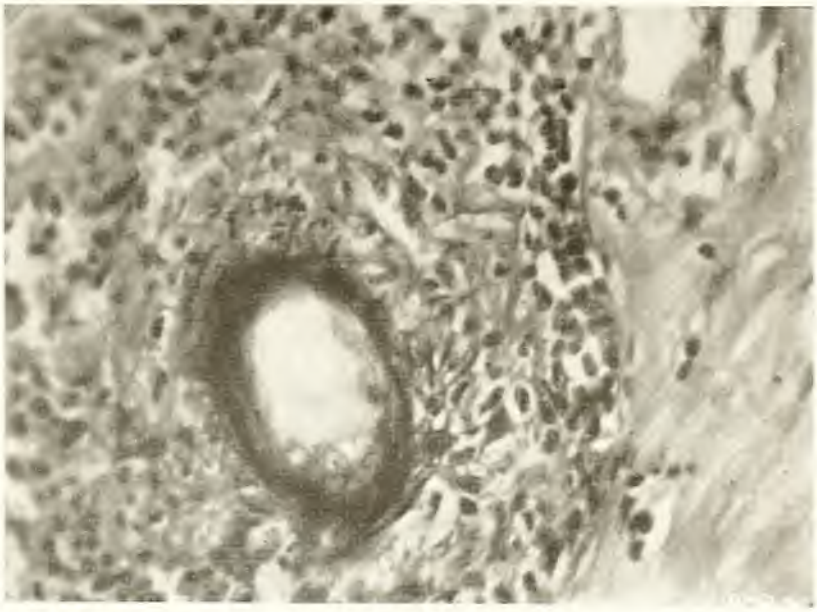

Fig. 7 — (Biopsy MAD 8830) — Arteriole showing total necrosis of its wall, as well as peripheric inflammatory process.
Stain: PAS and hematoxylin 620 ×

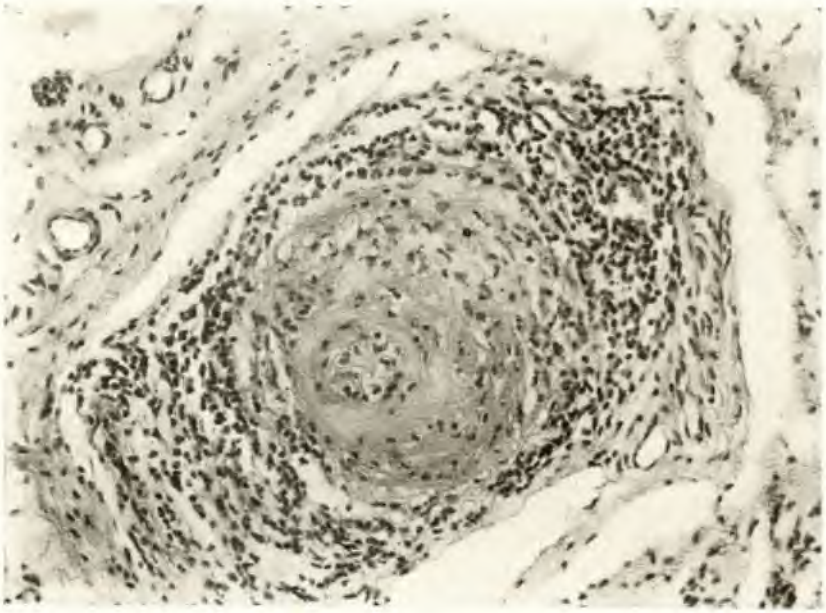

Fig. 8 — (Biopsy 7480) — Arteriole showing necrosis of its wall and adventitial inflammatory process. Endothelial cells tumefaction.
Stain: H.E. 500 ×

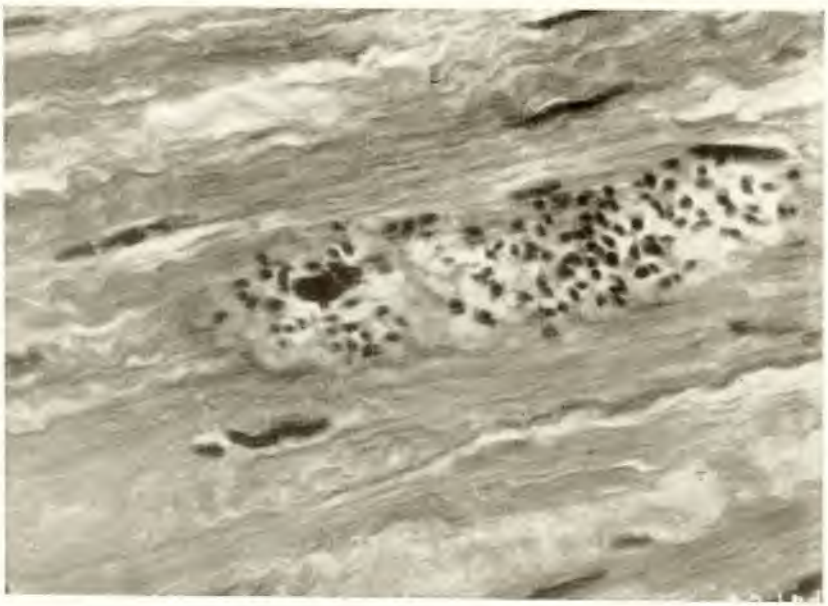

Fig. 9 — (Biopsy 3105) — Leishmania inside the smooth muscle fiber. No inflammatory reaction around it.
Stain: PAS and hematoxylin 620 ×

to the vessel. Moreover, it effects in the same case, various arterioles at the same time, with little phase variation from lesion to lesion.

COMMENTS

Most of the lesions mentioned above have already been described by different authors, but with a different interpretation. AMORIM & col.[1], based on HURST & RAKE [19, 20], suggested that the myositis was secondary to the plexus destruction. Recently KOEBERLE [25] has pointed out the prominence of the inflammation, which sometimes is granulomatous. He believes that this is the result of the *T. cruzi* action over tissues previously made hypersensitive to the parasite, a condition achieved at the chronic stage of Chagas' disease. The plexuses destruction is interpreted as the result of action of neurotoxin manifested at the acute stage of the disease, the substance being produced by the *T. cruzi*. According to this point of view megaesophagus and megacolon would be a part of a systemic chronic disease; in other words, Chagas' disease in its chronic stage. On the other hand, Chagas' disease should be considered primarily a disease of the parasympathetic system, which can be affected in its various locations [22, 24, 25].

We have no proofs yet regarding the presence of a neurotoxin. However, we do agree with Koeberle's interpretation of the myositis. It is difficult for us to understand a recurrent focal inflammatory process, sometimes located far away from the destructed and scarred plexuses, as being only secondary to their destruction. Moreover, it seems to us that we are dealing with a progressive disease, which affects the intestinal tract as a whole in different occasions. Highly suggestive of this hypothesis is the finding of a destruction of the gastric plexuses in some of our cases. Probably with more biopsies taken at different levels of the intestinal tract, we can prove anatomically the X-Ray findings of FONSECA & ALMEIDA TOLEDO [14, 16, 17, 44]. These authors have discussed the diffuse involvement of the alimentary tract in cases of megaesophagus and megacolon. Also VASCONCELOS & BOTELHO [45] have demonstrated gastric lesions in cases of megaesophagus. ETZEL & CORRÊA NETTO [9, 10]

have pointed out the frequent concomitant finding of megaesophagus and megacolon as well other "idiopathic" dilations in different systems and organs.

We have also studied two cases of oesophageal dyskinesia. One of them, after five years, presented a typical megaesophagus. The other is still in the functional period. However, both of them have showed the findings of myositis and focal destruction of plexuses which have been described above. FONSECA [15] believes that all transitions between oesophageal dyskinesia and megaesophagus are possible. The above mentioned findings are in agreement with this particular point of view.

CONCLUSIONS

The etiology and the pathogenesis of acquired megaesophagus and megacolon in Brazil are not settled yet. The earlier research workers on the problem, impressed with the plexus destruction, which was seen the first time by HURST & RAKE [20], considered megaesophagus and megacolon as a manifestation of vitamin B depletion [1, 9, 10, 12, 13, 39, 45]. That idea was based on experimental data. Myositis would be secondary to the plexus destruction.

Chronic Chagas' disease as *one* of the etiopathogenic factors of megaesophagus (so-called "mal do engasgo") was suggested for the first time by CHAGAS himself [6]. Lately epidemiology and serology [25, 26, 27, 37, 42] contributed to the idea, showing the high frequency of Chagas' disease (through a positive complement fixation test — Machado-Guerreiro's reaction) in patients with megaesophagus [37, 38]. Electrocardiographic alterations have also been seen in such patients [40]. The heart plexuses destruction [36, 40, 45], as well as the focal myocarditis occasionally seen in patients with megaesophagus, which were related to the vitamin B depletion, are now linked to the chronic Chagas' disease.

In sixty-three of our cases Machado-Guerreiro's reaction was performed being positive in 48 (76%). The other cases showed either negative or dubious results. Some cases had anti-complementary sera. Our morphological data are similar to the ones in the literature but we have seen in addition a necrotizing arteritis present in 9.8% of the cases. Unfortunately Machado-Guerreiro's test was done only in four of the nine cases with arteritis, being positive in three. The last one had an anticomplementary serum.

We were really impressed with the intensity and similarity of the myositis seen in megaesophagus with the one described in hearts of patients with the chronic form of Chagas' disease [34]. In one case, leishmanial forms were seen inside the muscle fiber. Another striking finding is represented by the tendency of the inflammatory process to be located around small vessels.

The different workers studying the etiopathogenesis of chronic Chagas' myocarditis [27, 29, 30, 35] consider allergy fundamental to explain the recurrence of the process [29, 35]. Also the vascular factor has been lately considered important to explain the pathogenesis of the myocardial lesion [2, 3, 4, 28, 30]. In spite of the fact that the arterial and capillary alterations described in human [8, 41] and experimental animal's hearts [28] are not morphologically identical to that seen by us in megaesophagus, we believe that there are many points of contact between chronic Chagas' myocarditis and the myositis seen in acquired megaesophagus in Brazil. Necrotizing arteritis seems to support the idea that the allergic process, which is known to be present in Chagas' disease [31, 32, 33] is also in megaesophagus. All the data above mentioned, together with the finding of leishmanial forms in one case seems to complete the similarity of both processes.

The mechanism of plexuses destruction remains unclear. We do not believe that arteritis can explain it, because it was found in a small percentage of the cases. Moreover, the study of early plexus lesions in the stomach has shown that destruction is reached through a real inflammatory process, ischemic neuronal necrosis not being the prominent finding.

A criticism which can be made regarding the necrotizing arteritis is that it can be a concomitant process of another etiology. Hypertension and rheumatic fever has been ruled out in all cases with arteritis, except one. Moreover, follow-up failed to show any other manifestation of primary vascular disease of the polyarteritis type. However, we do believe that only experimental studies can throw new light on the etiopathogenetic hypothesis and lesions above described. So far, we can say only that Chagas' disease *is probably one* of the factors for the development of megaesophagus and megacolon in Brazil.

RESUMO

Foi feito um estudo de 91 biopsias de músculo da cárdia de pacientes portadores de megaesôfago, operados pela técnica de HELLER-VASCONCELOS. Pudemos comprovar, sôbre o ponto de vista histopatológico, os seguintes fatos:

1 — Destruição dos plexos, por vêzes com formação secundária de neuromas e infiltrado inflamatório crônico em tôrno.

2 — Miosite intersticial crônica ou subaguda, com formação dos assim chamados "caminhos inflamatórios" (KOEBERLE), que vão até os plexos destruídos.

3 — Miosite focal, por vêzes de caráter granulomatoso.

4 — A estas lesões acrescentamos outra, até o presente não descrita, caracterizada por necrose parcial ou total de parede de arteríolas, ao lado de infiltrado inflamatório crônico linfo-histiocitário periadventicial. Em outras palavras, trata-se de verdadeira arterite necrotizante, *provàvelmente* do tipo alérgico.

5 — Temos evidências de ser o processo de natureza progressiva, pois o exame de cortes da musculatura gástrica em alguns casos demonstrou ora plexos normais, ora miosite com processo inflamatório em tôrno dos mesmos. Do mesmo modo, em alguns esôfagos que foram retirados totalmente, verificaram-se fases diferentes do quadro, as alterações mais antigas localizando-se junto à cárdia.

6 — Em um caso pudemos ver um ninho de leishmânias na musculatura lisa.

7 — Os dados epidemiológicos e mesmo anátomo-patológicos (KOEBERLE) de vários autores nacionais, são sugestivos no sentido de se tender a admitir a moléstia de Chagas como *um dos fatôres etiopatogenéticos* do megaesôfago no Brasil.

Nossos achados, *até certo ponto*, corroboram esta possibilidade. Supomos, entretanto, que existe um símile entre a miocardite chagásica crônica, onde, segundo MAGARINOS TORRES [20, 30], o fator alérgico desempenha papel fundamental, e a miosite com destruição de plexos vista nos casos de megaesôfago e discinesia esofágica. Corroborando esta possibilidade, que só poderá ser provada definitivamente através da patologia experimental, está o encontro de arterites, provàvelmente do tipo alérgico, em certas biopsias de megaesôfago.

8 — Nossos achados anátomo-patológicos corroboram os trabalhos de fisiologia radiológica realizados por FONSECA [14, 16, 17, 44], demonstrando que o megaesôfago é apenas uma das manifestações de um processo mais geral, que afeta diferentes porções do tubo digestivo.

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Addendum: — MAGARINOS TORRES (Mem. Inst. Oswaldo Cruz, 56:85, 1958) has shown arterial lesions in hearts of Cebus' monkeys experimentally infected with *T. cruzi*. The arterial lesions were also ascribed to hypersensitivity. Also KOEBERLE (Virchows Archiv, 330:267, 1957) has demonstrated arterial lesions in hearts of human beings with chronic Chagas' disease.