Enteromegaly and cardiomegaly in Chagas disease

FRITZ KÖBERLE

From the Medical School of Ribeirão Preto, São Paulo, Brazil

EDITORIAL SYNOPSIS Chagas disease due to a trypanosome infection may lead to extensive destruction of ganglion cells in the peripheral autonomic system and may result in gross enlargement of the oesophagus, colon, and heart. From studies on nerve cell counts it is concluded that the number of ganglion cells in the oesophagus must be reduced to less than half to produce functional disturbances in the oesophagus and to one tenth to produce a megaoesophagus.

Problems of terminology are discussed.

Megaoesophagus, megacolon, and dilatations of other muscular hollow organs are extraordinarily frequent in Brazil, so frequent that several authors have used the term endemic. In two towns of fewer than 50,000 inhabitants in the southern part of the state of Minas Gerais, Mineiro (1958) and Freitas (1950) found and published 1,514 and 2,000 cases respectively of megaoesophagus. This number is many times greater than the total number of cases in various European countries, and these figures alone are sufficient to suggest that in Brazil, or at least in parts of it, there must be a disease responsible for the extraordinarily high incidence of 'megas'. This suspicion has been expressed more than once, but could not gain acceptance in the face of the theory that these conditions were due to vitamin B1 deficiency (Etzel, 1935). Chagas (1916a and b) indeed expressed the view that the dysphagia observed by him after the acute phase of the disease might be the initial stage of megaoesophagus.

The 'megas' so often seen in Brazil are typical late manifestations of Chagas disease (Köberle, 1956a), and *Trypanosoma cruzi* infection gives rise to two fundamentally distinct disease processes (Köberle, 1959c): 1 Chagas disease in the strict sense, that is, infections with trypanosomes with an acute septic-aemic phase, passing after the development of specific resistance into a chronic phase with few parasites; 2 sequelae of Chagas disease, or late manifestations, which develop as a result of the extensive destruction of ganglion cells in the peripheral autonomic system and/or the central nervous system during the acute phase (Fig. 1). The destruction of ganglion cells is due to the liberation of a neurotoxin from the *Leishmania* forms dying in the neighbourhood of ruptured pseudocysts during the acute phase (Köberle, 1956d). In rats, Alcantara

FIG. 1. Diagram of the course of Chagas disease.

(1959) found up to 80% of the ganglion cells in the heart irreversibly damaged during this phase.

These considerations have led to a change of opinion regarding the nature and treatment of Chagas disease, in particular the part played by nerve lesions in its pathogenesis. Since *Trypanosoma cruzi* is chiefly a parasite of muscle, destruction of the ganglion cells is to be expected wherever nerve cells are to be found within or close to muscular tissue. This is especially true of the parasympathetic ganglion cells associated with the muscular hollow organs and heart. The ganglion cells of the sympathetic paravertebral chain, on the other hand, show only slight lesions, if any (Brandão, 1961). Since in Chagas disease there is more or less extensive destruction of the parasympathetic ganglion cells of the muscular hollow organs, it is possible to estimate the degree of denervation by counting the ganglion cells, and to investigate the possible consequences of this denervation. In the digestive tract, the parasympathetic system determines motility, secretion, and absorption. There are disturbances of

all three functions in Chagas disease, and Rezende (1959), on the grounds of our new concept of Chagas disease, has used the term 'forma digestiva' to sum up all these functional disturbances of the digestive tract. This study deals with the disturbances of motility and their consequences, because they are fairly easy to recognize morphologically, and can be detected even in the absence of corresponding clinical findings.

ENTEROMEGALY

The term 'enteromegaly' is suggested for all those dilatations of the muscular hollow organs which are not due to any obstruction, either mechanical or functional. Enteromegaly therefore includes all so-called idiopathic hypertrophies and dilatations, for which there are more than 50 different names, the best known being 'megaesophagus' and 'megacolon'. Terminology is important, for an unsuitable name may lead to completely erroneous conceptions of pathogenesis, which can even have adverse effects on the patient. The best example of misleading terminology is 'congenital megacolon', because it resulted, for over half a century, in the removal of a perfectly healthy colon, affected by purely secondary dilatation and hypertrophy. However, as early as 1898, Treves of London had obtained a complete cure in a case of Hirschsprung's disease by excision of the entire rectum, sigmoid flexure, and descending colon. After Dalla Valle, in 1920, had demonstrated the absence of ganglion cells in the distal colon, the existence of an 'aganglionic segment' was repeatedly confirmed, and was carefully investigated by Bodian and his collaborators (1949, 1951). Bodian therefore rightly maintained that the misleading term 'congenital megacolon' should be finally abandoned and Hirschsprung's disease used instead.

The names 'enteromegaly' and 'mega' should be reserved for all those conditions in which the dilated segment itself is diseased, and in this sense one might speak of 'idiopathic' dilatation. It will be objected that dilatation of a muscular hollow viscus and functional hypertrophy of the muscle can only occur above an obstacle to free passage. Lee and Bebb (1951) do not accept an idiopathic type of megacolon in this sense, and write: 'If such an interpretation were correct, it would represent the only instance known to medical science of a hollow viscus becoming chronically dilated and hypertrophied in the absence of obstruction'. And yet there exists a form of dilatation and hypertrophy in which the cause lies in the diseased viscus itself and may be called 'neurogenic dilatation and hypertrophy' (Köberle, 1957c). Examination of the function of the muscular hollow viscera shows it quite convincingly. The automatic

activity of the smooth muscle of the digestive tract is converted by the ganglion cells of Auerbach's plexus into coordinated peristalsis and adapted to the immediate local and systemic conditions. In this way the same contents entering the organ are passed out again after a certain time, brief for the oesophagus and longer for the stomach and large intestine. It will be understood without further explanation that any disturbance in peristalsis, especially if it leads to incoordination of the wave-like forward motion, will delay the passage of the contents, causing stagnation and retention, and necessarily also dilatation of the viscus. Since distension of the muscle fibres is the chief cause of hypertrophy, continuous dilatation and hypertrophy lead to the well-known mega formations based on a disturbance of the intrinsic innervation of the organ. This pathogenetic mechanism does not apply to the digestive tract only, but to all the muscular hollow viscera. Figure 2 shows the frequency of the various mega formations in 250 necropsies of cases of Chagas disease. It must, however, be stated that this clinical material shows that megaesophagus is more frequent than megacolon. In the post-mortem material megacolon, however, is the more frequent, because of spontaneous or post-operative fatal complications.

The necropsy statistics show clearly that megaesophagus and megacolon are far more frequent than mega formations in other hollow viscera, and the same applies to all clinical statistics. Since Chagas disease spreads by way of the bloodstream, it might be expected that the extent of denervation would be approximately the same in all the hollow viscera, or at least in those of a particular system of organs. A case in point was published in 1932 by

FIG. 2. Enteromegaly in 250 cases of Chagas disease.

Amorim and Corrêa Netto, who, in a patient with megaesophagus and megacolon, found lesions of Auerbach's plexus in the whole digestive tract, and not only in the oesophagus and colon. There must therefore be other factors than denervation in Chagas disease which favour mega formation or make it possible.

Several factors play a decisive part in the pathogenesis of enteromegaly. A functional disturbance cannot be detected or cause recognizable consequences unless some demand is made on the disordered function. Megacolon will not develop even in a severely denervated large intestine if the organ is excluded by a colostomy. Conversely, marked regression may occur in a megacolon in the section of the intestine which has been excluded for a few weeks before operation by a colostomy in the transverse colon. The contrast between the radiograph made before colostomy and the specimen obtained on resection a few weeks later is striking. In the rural population of Brazil, dysphagia occurs chiefly when eating cold rice, and since the transport of solids is a harder task for the peristalsis of a hollow viscus than the transport of fluids, it follows that dilatation is more frequent in the oesophagus and colon, which have to deal with solid material, than in the rest of the digestive tract.

A sphincter is by no means essential in mega formation, as is shown by the occurrence of megaduodenum and megajejunum, but some contributory importance must be attributed to a sphincter. The success of Heller's cardiomyotomy in certain cases confirms this hypothesis.

Finally, psychological influences, of which every

layman is aware in connexion with swallowing, must be mentioned. The case histories of patients with Chagas disease are full of statements which show the effect of mind on their symptoms. The remark by one patient with occasional dysphagia, that when his mother-in-law was in the house he could not even swallow coffee, is an illuminating example. It is understandable that the duration of the strain, as well as its intensity, is of decisive importance.

Whereas most sufferers from Chagas disease go through the acute phase in early childhood, the symptoms affecting the hollow viscera occur especially frequently after the twentieth year (Fig. 3). A longer or shorter period, depending on the degree of denervation, must pass before the functional disturbance leads to the development of a mega. The functional disturbance can, however, be observed immediately after the acute phase (Chagas, 1916a; Rezende, 1959). To what extent other factors favour the development of a mega is not yet known but it is certain that the intensity and duration of mechanical strains play a decisive role.

The finding that the mega formations in Brazil, and presumably also those which occur so frequently in the whole American continent up to the southern states of the U.S.A., are manifestations of Chagas disease, provides abundant material for tracing the development of these manifestations. In doing this, however, the criterion used must be functional, not morphological. The term 'aperistalsis', suggested by Brasil (1956), therefore seems to us the most suitable, because it correctly characterizes the functional disturbance which is ultimately responsible. If 'aperistalsis' is looked for by functional methods in

FIG. 3. Distribution of megacolon, megaesophagus, bronchiectasis, and megastomach in 250 cases of Chagas disease at various ages.

various hollow viscera in apparently healthy patients with Chagas disease, it is found in about one fifth of the cases. In his diagnosis, the clinician should pay attention to the demonstration of aperistalsis rather than to the morphological final mega stage.

QUANTITATIVE INVESTIGATIONS ON THE DEGREE OF DENERVATION OF HOLLOW VISCERA

To determine the number of ganglion cells in the intramural plexus, rings 3-4 mm. thick were taken at various levels of the oesophagus, colon, and bronchi from normal individuals and patients with Chagas disease. After embedding, they were cut into serial sections, each 7 γ thick, and every seventh section was selected (to avoid counting ganglion cells twice). Twenty sections were taken from each block, making a total thickness of 980 γ , that is approximately 1mm. Because of the irregular distribution of ganglion cells in the bronchi, the counts were made in a ring 1 cm. thick.

Tables I-III and Figs. 4, 5, and 6 show the results of counts in the intramural nervous system of the oesophagus, bronchi, and colon. Particularly striking cases with severe dilatation have been selected, and the denervation, especially in the oesophagus, is therefore unusually marked. However, it appears from counts in cases of Chagas disease without mega-oesophagus that even considerable denervation does not necessarily produce dilatation and hypertrophy. In such cases there are disturbances of motility which can be detected by functional examination, as Godoy and Haddad (1961) showed in 17% of their asymptomatic cases of Chagas disease. Ganglion cell counts have been made in over 40 control cases and in an equal number of Chagas disease, and our investigation, which is not yet concluded, has given the impression that the number of ganglion

FIG. 4. Number of ganglion cells in the lower third of the oesophagus.

TABLE I

NUMBER OF GANGLION CELLS IN THE MYENTERIC PLEXUS IN A RING OF OESOPHAGUS 1 MM. THICK IN 10 NORMAL CASES.

	Upper Third	Middle Third	Lower Third
	159	814	874
	629	841	897
	322	689	976
	576	734	989
	427	678	1,007
	456	731	1,026
	307	728	1,048
	487	691	1,064
	640	1,032	1,072
	452	850	1,086
Average	445	778	1,003

TABLE II

NUMBER OF GANGLION CELLS IN CHAGAS DISEASE WITHOUT MEGAOESOPHAGUS

	Upper Third	Middle Third	Lower Third
	0	3	97
	0	94	101
	33	75	173
	6	145	234
	44	251	434
	47	407	445
	148	210	535
	200	437	570
	328	554	640
	415	439	680
Average	122	261	391

TABLE III

NUMBER OF GANGLION CELLS IN CHAGAS DISEASE WITH MEGAOESOPHAGUS

	Upper Third	Middle Third	Lower Third
	0	0	0
	0	0	0
	0	0	0
	0	0	0
	0	0	0
	0	0	0
	0	0	0
	0	2	5
	0	7	8
	1	6	14
Average	0.1	1.5	2.7

FIG. 5. Number of ganglion cells in the right bronchus.

FIG. 6. Number of ganglion cells in Auerbach's plexus in various parts of the large bowel in five normal cases and five cases of Chagas disease. Note the more or less uniform diminution in the number of ganglion cells in the various parts in individual cases.

cells must be reduced to less than one half to produce functional disturbances in the oesophagus, and to one tenth of the normal to produce a megaesophagus. The 'tolerance' of the oesophagus to reduction of the intramural ganglion cells is therefore fairly wide. The 'tolerance' of the colon seems to be less, as Figure 9 shows clearly. It is not easy to explain this difference, because denervation is not the only pathogenic factor in enteromegaly. The difference is perhaps partly due to the presence in the oesophagus of a fairly large proportion of striated muscle, and to the fact that gravity to some extent assists the act of swallowing, but subjective factors are certainly

concerned also. Dysphagia and retention of food in the oesophagus are always felt to be unpleasant, and the patient tries to reduce the disturbance in swallowing by every possible method. Defaecation is quite another matter, and patients who have no bowel movements for two or three months are by no means rare. There are even patients who do not defaecate for four, five, or even six months. It is not surprising that in these circumstances the colon, which may hold over 30 litres, is enormously overloaded, and even moderate denervation must lead to a huge megacolon.

The complex problem of enteromegaly cannot,

therefore, be simplified by considering it simply as a problem of denervation, or by trying to correlate the degrees of denervation and dilatation. In Chagas disease it is, however, possible to detect and measure lesions of the autonomic nervous system without the well-known 'erratic' impregnation techniques, and avoiding, to a very great extent, all subjective criteria, and also to demonstrate the pathogenic significance of these lesions in large series of cases. In these ganglion cell counts qualitative changes in the cells have been disregarded because they were constantly seen, and suggest that the *de facto* denervation can only be greater than that observed by us.

Chagas disease is the cause of the Brazilian endemic megas, and this aetiology applies to the majority of American megas. It has been, and is still, objected that so-called 'acquired megas' occur in Europe and in other places where Chagas disease does not exist. As a result of many years' work in Europe, especially at the Pathological Institute in the University of Vienna with its vast necropsy material, it can be said that Chagas disease does not exist in Europe and for that very reason megas are very much rarer than in Brazil. Besides, these arguments miss the point of the problem, in that they look upon megas as a disease and not as a disorder or syndrome, that is, as a consequence of a lesion of the central nervous system. In opposition to this view it is stated that megas have been described in which the intramural nervous system appeared to be intact. In this connexion it may be noted that many of these are cases of Hirschsprung's disease, observed when the secondarily dilated part of the colon was excised as a megacolon, and in this segment of intestine the intramural nervous system is not affected. Other findings merely refer to the presence of ganglion cells, no quantitative investigation of serial sections having been made. There are also cases caused by disturbances in intrinsic innervation, without any morphologically recognizable changes in the intramural nervous system. Cases of this kind have been described by Siegmund (1935) in Parkinsonism treated for many years with atropine, that is to say, in patients whose parasympathetic intestinal innervation has been suppressed pharmacologically. Finally, it is conceivable that infections or poisoning (war gases) may produce similar functional lesions in the autonomic nervous system, with little or no morphological change. In certain circumstances it may therefore be extremely difficult, if not impossible, for the pathologist to detect morphological evidence of the disturbance of innervation responsible for the condition found.

There has been much discussion of the question whether atony or hypertonia of the mural muscula-

ture plays the decisive part in the pathogenesis of enteromegaly. In the advanced stage, it is often impossible to decide, because atony is nearly always present. Whereas in cases due to atropine there is always primary atony, the condition in Chagas disease is always due primarily to hypertonia. This can be deduced purely theoretically from Cannon's law of denervation, and can easily be demonstrated in numerous patients with Chagas disease. It has been clearly shown in the oesophagus by Vasconcelos and Botelho (1937), Brasil (1956), Rezende (1956), and Godoy and Haddad (1961).

Thus in Chagas disease a more or less marked decrease in the number of parasympathetic ganglion cells in the hollow viscera leads in time because of permanent over-loading to enteromegaly, which may be limited to a single organ or appear in all kinds of combinations.

CHAGAS CARDIOMEGALY

Heart disease is by far the most frequent manifestation of Chagas disease. It was described in a masterly manner by Chagas himself in many papers (1909-1920) and by Chagas and Villela (1922). The classic descriptions of Chagas have been fully confirmed on countless occasions. As regards pathogenesis, the opinion was generally held that the disease was a chronic myocarditis. It would be far beyond the scope of this paper to discuss the pathogenesis of this remarkable heart disease in detail. Clinically, the disease is characterized by disturbances in stimulus formation and conduction (Chagas) and sometimes enormous enlargement of the heart, which cannot be explained by the existing 'tonogenic' and 'myogenic' theory. The valves are quite normal in these hearts. The blood pressure in Chagas disease may be raised but is usually considerably lowered. Foci of parasites and inflammatory reactions are extremely rare in the chronic phase, and cannot often be found even if hundreds of serial sections from all parts of the heart are examined. It is true that in advanced cases there are necrobiotic and necrotic lesions of the heart muscle but these are the expression of coronary insufficiency, that is, results of the cardiac enlargement and not causes of it. Besides, such lesions are often absent, or limited to the field of the left coronary artery whereas the dilatation is more marked on the right. Routine examination of the heart thus often fails to disclose any reason for the often severe dilatation and hypertrophy of the heart.

The cause of the cardiomegaly in Chagas disease is thought to be the same disturbance of intrinsic innervation as described in enteromegaly. The dilatation and hypertrophy of the heart are thus 'neurogenic' (Köberle, 1957a). As regards pathogene-

sis, the same arguments apply as in enteromegaly. The automatic action of the heart is adapted to the needs of the moment by the autonomic nervous system. Any disturbance of this regulation must give rise, in the long run, to dilatation, with distension of the fibres and subsequent hypertrophy, especially if there is overloading in the form of an increased amount of residual blood. A vicious circle of dilatation and hypertrophy leads finally to severe cardiomegaly, with characteristic hypoxaemic lesions of the left ventricle, and, in particular, to typical aneurysms of the apex of the left ventricle. The importance of the duration and severity of the strain in the pathogenesis of this form of cardiomegaly is shown by the fact that chronic cardiopathy in Chagas disease is two or three times as common in men as in women.

As in other hollow viscera, the parasympathetic ganglion cells of the heart are seriously damaged in the acute phase of Chagas disease. The degree of destruction was determined by cutting serial sections of the posterior wall of the right atrium between the superior and inferior vena cava in the manner already described. Here again, all identifiable ganglion cells were counted, whether they showed degeneration or not, so that the degree of degeneration observed is obviously less than the true degree. Because of the observed loss of parasympathetic ganglion cells in Chagas disease, it may be called 'cardiopathia parasympathicopriva' (Köberle, 1959b). The course, clinical symptoms, frequency of sudden death, and the very unusual morphological findings stamp Chagas cardiopathy as a disease *sui generis*. Chagas therefore spoke with every justification of a new chapter in human pathology, of the greatest pathogenic curiosity, for he already suspected that the nervous system played a part in the pathogenesis.

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