Several necropsy studies in humans have demonstrated intense cardiac neuronal depopulation in the various Chagas' disease stages\textsuperscript{1,2-5}. Experimental work with animal models of the disease\textsuperscript{1,6-13} also confirmed these findings.

Despite these findings, mostly in the cardiac, esophageal and colon tissue\textsuperscript{5,14,15}, no correlation exists between the intensity of neuronal destruction and dilation of the heart or other microscopic indices of myocarditis in the chronic phase\textsuperscript{14}. Histopathologic foci of damaged nervous tissue are found in a diffuse and irregular distribution. Neuronal parasitism, with periganglionitis and degenerative abnormalities in Schwann cells and nervous fibers being prominent manifestations. Although the cardiac parasympathetic nervous structures seem to be more vulnerable, paravertebral sympathetic ganglia destruction has also been documented\textsuperscript{4}. Autopsy studies in chagasic individuals who were asymptomatic during life and suffered from accidental death show that marked neuronal depopulation may be present in absence of any signs of cardiac disease\textsuperscript{14,16}. Thus, some chagasic patients have marked cardiac autonomic denervation at an early stage in the natural history of the disease.

Although the mechanisms responsible for the aggression to the autonomic nervous system in the early stages of Chagas' disease remain undetermined, it seems reasonable to assume that the neuronal destruction may be related to the immunoinflammatory reaction unchained by the parasite presence in the muscle lying in close vicinity to the neuronal ganglia. The notion that parasite strain, environmental or host-parasite interaction are important factors in determining the extent of neurotropism is supported by findings from experimental and clinical studies\textsuperscript{16,17}.

In correspondence to these anatomic alterations, conspicuous abnormalities of parasympathetic and, to a lesser extent, of the sympathetic cardiac autonomic control have been described in both experimental models and in human studies\textsuperscript{10,16-20}.

Parasympathetic dysfunction is demonstrated through impaired chronotropic responses to a variety of physiologic - Valsalva maneuver, isometric and dynamic exercise, passive postural change, measurement of respiratory sinus arrhythmia and RR variability during Holter monitoring - and pharmacologic stimuli - atropine, nitroglycerin and phenylephrine injection\textsuperscript{16,17,19,20}.

Impairment of the parasympathetic control of heart rate has also been demonstrated in chagasic patients with sole digestive involvement\textsuperscript{20}. Moreover, recent investigations provide evidence that in chagasic patients with the digestive forms of the disease, parasympathetic impairment occurs despite the absence of any signs of left ventricular dysfunction, but bears no correlation to isolated right ventricular involvement, as shown by radionuclide angiography\textsuperscript{18}.

Sympathetic derangements are more difficult to demonstrate in chagasic patients. While it is possible to observe deficient late chronotropic responses to head-up tilt, maximal exercise fails to disclose abnormal heart rate changes\textsuperscript{16}. This reflects the clear predominance of the damage of intramural cardiac, esophageal and colonic parasympathetic system (as compared to that of the sympathetic neurones), in chagasic patients as well as in animals experimentally infected with the \textit{T. cruzi}.

There is some discrepancies in the results of the assessment of the vascular control in chagasic patients\textsuperscript{16}. However, it is relevant to point out that if any adrenergic vascular control abnormality occurs at all in patients with Chagas'
disease, such derangement neither is correlated with any symptoms, nor causes postural hypotension. Thus, in contrast with other disorders with widespread involvement of the neurovegetative system (e.g. diabetes mellitus), in Chagas' disease no true clinical syndrome of cardiovascular adrenergic dysautonomia has ever been described.

Recent studies, employing lower body negative pressure, have shown impaired reflexes mediated by cardiopulmonary receptors in chagasic patients without heart failure. Also, investigations with isocapnic hypoxia and hypercapnia plus hyperoxia indicate that chagasic patients without wall motion abnormalities have exacerbated sympathetic responses to stimulation of peripheral chemoreceptors and reduced central chemosensitivity.

Although not specific of Chagas' disease, the autonomic impairment is more severe than in other cardiac diseases. Direct comparative studies have shown much less severe degrees of parasympathetic denervation in rheumatic disease, idiopathic dilated cardiomyopathy, hypertension, and endomyocardiofibrosis.

Parasympathetic denervation is widely accepted as the essential pathogenetic mechanism of chagasic megaesophagus and megacolon. Similarly, because of the early, intense, and largely predominant cardiac parasympathetic denervation a neurogenic theory of Chagas' heart disease has been proposed: a long lasting autonomic imbalance would lead to a catecholamine-induced cardiomyopathy. Also, chagasic patients exhibiting abnormal baroreflex control of the heart rate are deprived of an important homeometric mechanism of regulation. This could, in theory, contribute to myocardial dysfunction and ventricular dilatation.

However, various lines of evidence militate against the concept of neurogenic derangements as the main pathogenetic mechanism of Chagas' heart disease. First, the prevalence and intensity of this abnormality are quite variable; differences in T. cruzi strain and/or regional environment are likely causes for variable neurotropism observed in several regions. Second, a mismatch between the presence of autonomic denervation and ventricular dysfunction is often observed. Third, studies aimed at investigating the presence of autonomic dysfunction and early contractile impairment have failed to show any significant association between these two disturbances.

Nevertheless, a critical appraisal of this issue should consider that in all investigations mentioned above the autonomic cardiac autonomic function was always assessed through tests of heart rate control. Hence, evidence of early nervous damage possibly occurring at the ventricular myocardial level, may have been overlooked.

A more appropriate insight into this aspect was obtained with recent investigations using I-MIBG scintigraphy for evaluation of myocardial sympathetic nerve terminals. Segmental areas of sympathetic denervation were detected in a high proportion of patients even in the indeterminate phase of Chagas' heart disease. This is the first functional evidence of early cardiac sympathetic impairment preceding left wall motion abnormalities in the indeterminate phase of chronic Chagas' disease. Figure 1.
Increased $^{123}$I-MIBG washout rate was also observed in patients with normal segmental ventricular function\textsuperscript{30}. Figure 2. Both types of disturbances correlate with the occurrence of regional perfusion defects and with the progression of myocardial damage as reflected by wall motion impairment.
The washout abnormalities could be due to early increased cardiac sympathetic activity, lending support to the neurogenic theory as stated above. However, alternative hypotheses should be considered: inflammatory and/or ischemic mechanisms, as discussed in another talk of this session, could possibly be implicated in the genesis of the tracer washout disturbances. They could also be caused by competition between the radiotracer and endogenous substances acting upon the neurotransmitter receptors of the sympathetic nerve terminals.

In plausible concordance with this last hypothesis recent reports have documented in patients with Chagas' disease the existence of circulating antibodies which bind to adrenergic and cholinergic receptors of lymphocytes and myocardium \[31-35\]. Studies focusing on antibodies against heart adrenergic and cholinergic receptors have shown their ability to trigger physiologic, morphologic, enzymatic and molecular alterations, potentially leading to cardiac damage \[33-35\]. Deposit of autoantibodies upon the myocardial neurotransmitter receptors could induce their desensitization or down-regulation and cause progressive denervation. Such mechanisms could represent an elusive but significant link between denervation and autoimmune aggression as pathogenetic factors in Chagas' heart disease.

It is possible to conclude, therefore, on the basis of the evidence available, that the cardiac dysautonomia (mainly parasympathetic) found in Chagas' disease has a component that is irreversible and primarily related to the host-parasite interaction mechanisms outlined above. However, Chagas' heart patients will also present the nonspecific autonomic derangements and neurohormonal activation that are associated with progression of left ventricular dilatation and failure. This later aspect has relevant implications because the neurohormonal activation occurring in chagasic patients with myocardial damage and left ventricular dysfunction should be therapeutically antagonized as an attempt to favorably influence the natural history of Chagas' disease \[26\]. In this regard, prospective studies involving therapy with ACE inhibitors in small groups of chagasic patients with heart failure showed promising preliminary results for the control of symptoms \[17\]. Although no longterm controlled studies have been reported about the impact on survival of chagasic patients treated with ACE-inhibitors or any other pharmacological interventions, there is no reason to believe their potential beneficial effect would be any different from that observed in heart failure due to other etiologies \[27\].

*In summary, the neurogenic theory remains a very debatable issue. Its prognostic implications have never been assessed through appropriate follow-up studies. Finally, the hypothesis implicating autonomic impairment in triggering sudden death, derived from pathological reports of small, highly denervated hearts found at autopsy in chagasic patients who died suddenly \[14,16\], remains entirely speculative \[16\].*

### References