Pathophysiology of achalasia of the cardia

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Summary

The symptoms and signs of achalasia are due to the loss of ganglion cells in the body of the oesophagus, leading to dilatation and loss of peristaltic activity. The data pertaining to the lower oesophageal sphincter are still somewhat conflicting. The ganglion cells may be absent, but pharmacological evidence suggests denervation to be pre-ganglionic. The classical view of a normotensive, non-relaxing achalasic sphincter has been challenged by recent observations which suggest the presence of a hypertensive, partially relaxing sphincter, which is supersensitive to gastrin and acetylcholine.

THE cause of achalasia remains unknown, and there is no universal agreement on the histopathological and manometric findings. One of the reasons for discrepancies between results from different laboratories may be that a progressive pathological process is associated with varying features during the course of the disease. The stage at which the patient is studied may therefore influence the nature of the observations: progressive dilatation of the oesophagus in achalasic patients is one example. The mere length of history is a poor guide to the stage the disease has reached, because the rate of progression is variable. It is sometimes assumed that achalasia is a homogeneous clinical entity: this may not be so in practice. So far, no unequivocal diagnostic test has emerged although the diagnosis can be confidently established on clinical grounds in a typical case.

It is generally accepted that the signs and symptoms of achalasia stem from denervation of the oesophagus, but the site at which the denervation takes place is not entirely settled. Abnormalities of the dorsal nucleus of the vagus have been reported in a small number of cases (Cassella *et al.*, 1964), but this conflicts with good histopathological evidence that achalasia is associated with the degeneration of the myenteric ganglia in the body of the oesophagus (Hurst and Rake, 1929-30; Cross, 1952; Adams *et al.*, 1961).

The data pertaining to the lower end of the oesophagus and particularly the sphincteric zone, are more conflicting. Adams *et al.* (1961) reported that

the ganglion cells of the myenteric plexus from that region were normal but sometimes reduced in number. This observation was not confirmed in another study, in which ganglion cell counts were performed on sphincteric tissue from fourteen achalasic patients; nine had none and a further three had very few, ganglion cells. Where ganglion cells were present, they were invariably abnormal, whilst the myenteric plexus of nerves showed marked fibrosis and lymphocytic infiltration (Misiewicz *et al.*, 1969).

In vitro pharmacological analysis of responses of achalasic sphincteric muscle shows differences from non-achalasic oesophageal tissue. Stimulation of intrinsic nerves or ganglia with drugs (nicotine or dimethylphenylpiperazinium, DMPP) resulted in β -adrenergic relaxation of the non-achalasic muscle strips; this was absent in the achalasic group. Thirty per cent of achalasic strips showed cholinergic contractions with nicotine; in the control strips such contractions were never seen without prior eserization (Misiewicz *et al.*, 1969). These data suggest that β -adrenergic activity, which may be important in sphincteric relaxation, is lost in achalasia. Moreover, in at least some patients hypersensitivity to acetylcholine is present. The site of denervation in achalasia was further investigated by workers using intraluminal manometry in the intact patient. Direct cholinergic stimulation with betamethacholine (Cohen and Guelrud, 1971) and the effects of a cholinesterase inhibitor edrophonium (Cohen, Fisher and Tuch, 1972) were studied. The achalasic sphincters were hypersensitive to betamethacholine whilst edrophonium increased the sphincteric pressure. The observations with betamethacholine were interpreted as indicating the presence of denervation supersensitivity, whilst the preservation of response to the cholinesterase inhibitor suggested the presence of intact post-ganglionic cholinergic nerves, implying that the site of denervation in achalasia may be preganglionic.

Earlier manometric studies performed with unperfused open-ended tubes or with small balloons established a sequence of motor abnormalities in achalasia of the cardia. The orderly progressive peristaltic contractions of the body of the oesophagus

are replaced by non-progressive simultaneous contractions. The pressure in the lower oesophageal sphincter is normal and the sphincter fails to relax during swallowing, although the after-contraction remains (Creamer, Olsen and Code, 1957; Edwards and Rowlands, 1959). The normal sphincteric pressures recorded by the then available methods accorded with Hurst's (1929-30) view, that the term cardiospasm was wrong and that the condition was correctly termed achalasia, i.e. failure (of the sphincter) to relax. These ideas were reinforced by the absence of any resistance to the passage of oesophagoscopes or mercury bougies through the achalasic sphincter.

This classical concept has been challenged by more recent studies with perfused open-ended tips. Studied with this technique, the achalasic sphincter appears to be markedly hypertensive and to retain a limited, but distinct ability to relax. Despite high sphincteric pressures, serum gastrin levels were normal in nineteen patients with achalasia and the sphincter relaxed when the gastric antrum was acidified. Supersensitivity of the achalasic sphincter to exogenous gastrin I was also demonstrated (Cohen, 1965; Cohen, Lipshutz and Hughes, 1971).

If these interesting observations are confirmed, it looks as if cardiospasm may be restored to respectability. On the other hand, Heitmann, Espinoza and Csendes (1969) using perfused tubes recorded normo-tensive sphincter pressures in all of sixteen patients with symptoms and radiological features of achalasia. In another study, only three of ten achalasic patients had sphincteric pressures above the normal limit of 20 mm Hg ($n=48$), established in those authors' laboratory (Heitmann and Wienbeck, 1972). In Cohen's *et al.* (1971) hands, the upper limit of normal ($n=20$) was some 35 mm Hg and all but five of the nineteen achalasic patients were above that range.

Be this as it may, there is little doubt that following either cardiomyotomy or pneumatic dilatation, the majority of patients enjoy a marked relief of their

dysphagia. The fall in lower oesophageal sphincteric pressure after dilatation has been well documented (Vantrappen *et al.*, 1971; Heitmann and Wienbeck, 1972).

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