Pathophysiology and Clinical Presentation of Achalasia

RICHARD EARLAM

Achalasia of the oesophagus is a disease which has achieved more importance than would be expected, considering its extreme rarity. This is due partially to the excitement of seeing a large dilated oesophagus on x-ray but mainly because it demonstrates what can go wrong with normal physiology. The healthy oesophagus consists of a hollow muscular tube closed by a sphincter at each end, and is normally kept completely empty by a primary peristaltic wave which sweeps the lumen clear after each swallow. The cricopharyngeal sphincter prevents air entering when one breathes and the lower oesophageal sphincter stops the reflux of gastric contents. A secondary peristaltic wave can occur in response to distension by refluxed gastric contents and this is an additional mechanism to keep the oesophagus empty. In achalasia there is retention of food and drink in the body of the oesophagus and the normal reflexes for completely clearing the lumen are absent. There are no peristaltic waves in the body of the oesophagus and the lower oesophageal sphincter fails to relax in response to each swallow. These abnormalities are due to the loss of ganglion cells in Auerbach's plexus. The denervated muscle can still contract, but it is inefficient and incoordinated.

INCIDENCE

Achalasia affects males and females equally. It occurs in all races and does not predominate in white Caucasians alone. The high incidence in South America, especially in certain parts of Brazil, is due to Chagas' disease, an endemic disease caused by an infection with Trypanosoma cruzi. Otherwise, throughout the world the incidence of patients diagnosed is approximately 1:100 000 (Earlam, Ellis and Nobrega, 1969). The majority present between the ages of 35 and 45, having had their symptoms for about five years, although 20 per cent have a one-year history and 20 per cent longer than 10 years (Ellis and Olsen, 1969). In about 10 per cent the disease commenced in childhood. Neonates have been described but so have people in their seventies. There is no evidence of any outbreaks suggesting an infective origin and there are no definite familial or hereditary influences in the few low density epidemiological studies available, although a few siblings have
been affected. Man's best friend, the dog, may also suffer from achalasia. In short, achalasia is one of the classical diseases of unknown aetiology that occurs entirely by chance.

GROSS PATHOLOGY

The typical autopsy appearance of the oesophagus is of a thin-walled elongated bag tapering down to the narrow gastro-oesophageal junction. Retained contents are present instead of the normal emptiness. Although such specimens predominate in pathology museums they represent the end-stage of the disease when the musculature has given up its struggle to empty the lumen and has atrophied. There is always dilatation but the muscle wall may be normal. In the sphincter region it can even be thickened. The epithelium may be ulcerated and in about one per cent there is a squamous-cell carcinoma. It has been estimated that this rare change requires at least 20 years of antecedent history (Pierce, MacVaugh and Johnson, 1970). It has been calculated that the chance of a carcinoma developing is increased by seven times in achalasia (Joske and Benedict, 1959). The carcinoma is always squamous-celled, occurs in the body of the oesophagus, and is diagnosed late because it is asymptomatic or causes symptoms that cannot be differentiated from those in achalasia. It can occur even after a Heller's myotomy (Just-Viera and Haight, 1969). For some unknown reason the association of carcinoma with achalasia is commoner in Europe (up to 20 per cent in one series; Ellis, 1960) than in the United States, where only 0.5 per cent developed carcinoma (Wychulis et al, 1971).

MICROSCOPY

In achalasia there are always changes in the ganglion cells of Auerbach's plexus, situated between the inner circular and outer longitudinal layers of muscle (Smith, 1970). These intrinsic neurones may be completely absent (Figure 1) or reduced in number, with actual evidence of their degeneration. Other changes in Auerbach's plexus are infiltration with nonspecific round cells and fibrosis. The body of the oesophagus is always affected and this includes not only the lower smooth muscle part but also the upper one-third where there is striated muscle, innervated by the vagus. These changes may also affect the lower oesophageal sphincter and in rare cases extend on to the stomach. Correlation of the extent and severity of the ganglion cell changes with the clinical picture is a controversial subject. In general terms round-cell infiltration occurs early, and fibrosis in patients with a long history. Similarly, extension to the sphincter and stomach correlates with the more severe gross pathological changes.

In the past, ganglion cells have been subdivided on the basis of their morphological and silver staining appearances into motor, with one large axon, and sensory, with multiple dendrites. A recent concept is that Auerbach's plexus is predominantly motor, whereas Meissner's plexus, the neural plexus situated under the mucosa deep to the muscularis mucosae, is mainly sensory. In the oesophagus, where peristalsis is both fast and motor
activity almost independent of any afferent input, the sensory side and Meissner's plexus are usually absent. Changes in ganglion cells can therefore only be found from a muscle and not an epithelial biopsy. This is in contradistinction to Hirschsprung's disease where a mucosal biopsy may be of use clinically because ganglion cells can be shown to be absent in Meissner's plexus.

Figure 1. Auerbach's plexus, between the two muscular layers, contains no ganglion cells.

Muscle changes (Harrison, 1969) are present in the body of the oesophagus and the lower sphincter (Figure 2). By light microscopy this appears as a nonspecific sclerosis (Alnor, 1958). With electron-microscopy, changes can be demonstrated in individual muscle cells and the normal low resistance connections between muscle cells, called nexuses, are lost. A nexus is the smooth muscle equivalent to the intercalated disc that can be seen by light microscopy in cardiac muscle, but it is so small that it can only be seen with an electron-microscope. The significance of these muscular changes is not clear. There is certainly more damage than would be expected from simple denervation alone.

Apart from the pathology in the ganglion cells, there are also changes in the preganglionic fibres and their central nuclei (Figure 3). Degeneration of individual axones in the trunks of the vagus has been found with light and electron-microscopy (Cassella et al, 1964). It is known that the vagus is predominantly an afferent nerve at the level of the diaphragm, but there is no evidence as to whether the degenerating fibres are motor or sensory. Central changes in the dorsal motor nucleus of the vagus and in the nucleus ambiguus,
responsible for the motor innervation of the smooth and striated muscle portions of the oesophagus respectively, are found in the medulla oblongata (Cassella et al, 1964). It must be emphasised that the reduction in neurones occurs in two different isolated nuclei situated on either side of the medulla, and the changes in the nerve trunks are in both the right and left vagus. It is therefore extremely unlikely that such widespread preganglionic changes would result from one central lesion.

**AETIOLOGY**

The motor disturbances in achalasia can be explained by the effect of denervation on the smooth muscle of the body of the oesophagus and the lower sphincter, but the cause of the ganglion cell loss is unknown. Most of the earlier theories suggested local destruction due to toxins, nerve gases, infections, vitamin deficiencies and local inflammation. Infections are unlikely to affect only one part of the gut and Chagas’ disease provides no exception (Earlam, 1972b). In this disease the trypanosome enters the intermuscular lymphatics and either by local effect, inflammation or toxins, destroys the neurones which are also there. The process may take up to 30 years. It affects all the gut at the same time, but because of local differences in function the colon is enlarged about six times more frequently than the oesophagus. Even distension itself was proposed as a way of destroying...
ganglion cells with sublime disregard of Hirschsprung's disease in which the enlarged portion of the gut contains perfectly normal ganglion cells. However, from the previous section it should be apparent that the ganglion cell changes do not exist in isolation. There are muscular abnormalities as well as a reduction in the number of ganglion cells in the oesophagus itself.

and then a whole series of preganglionic changes, so the disease should be analysed in the same fashion as any neurological disorder. Viewed neurologically there are two explanations; either (1) the peripheral ganglion cells are primarily affected and the preganglionic neurones disappear secondarily due to retrograde degeneration, or (2) the central changes are primary and the peripheral loss of ganglion cells occurs secondarily because of tran-

Figure 3. A summary of all the pathological changes in achalasia including those in the brain stem, vagus nerves, ganglion cells and muscle.
synaptic degeneration. Transynaptic degeneration does not usually occur. Viewed teleologically, this means that when preganglionic fibres are destroyed, the intrinsic neurones are quite happy to go on functioning regardless of the loss of central control. This is shown very easily by a simple experiment. Vagotomy is never followed by loss of ganglion cells. On the other hand, retrograde degeneration, which would occur if Auerbach’s plexus were primarily destroyed, has been demonstrated experimentally and could account for the widespread central lesions found in achalasia. Although the central changes in achalasia have only recently been demonstrated, this has in effect served to emphasise that the primary changes must be in the wall of the oesophagus itself and not in the brain. Confirmation that the primary pathology must be in the oesophageal wall also comes from Chagas’ disease, since central lesions in the dorsal motor nuclei of the vagus have been demonstrated as a secondary effect subsequent to the trypanosomal destruction of ganglion cells (Lopes, Tafuri and Chapadeiro, 1969).

One possible method of destroying the intrinsic nerve cells is by ischaemia (Cannon and Burket, 1913). The principle is based on the fact that of the four basic tissues — epithelium, muscle, connective tissue and nerve — the latter is the most sensitive to anoxia and is also the only one unable to regenerate. It follows that an infarct, producing temporary ischaemia for four hours is enough to kill neurones and could cause the primary ganglion cell loss and the muscle changes, leaving other tissues to regenerate. The author has suggested that this could have occurred in utero due to an excess of the normal rotation of the gut while there is still a large umbilical hernia (Earlam, 1972a). The evidence is all circumstantial; there is no definite proof for this hypothesis although it fits most of the facts. The destruction of ganglion cells in achalasia still remains one of nature’s most perfect crimes, completely unsolved.

**MANOMETRY**

Oesophageal pressure studies have revolutionized our knowledge of achalasia. Although the majority of patients are diagnosed by radiology, doubtful patients ideally should have the benefit of manometry so that an accurate diagnosis can be made. On swallowing there is normally a peristaltic wave which passes from top to bottom of the oesophagus sweeping it clear. In achalasia simultaneous waves are recorded (Figure 4a) and if any one peristaltic wave is found the diagnosis must be rejected. The lumen is dilated and contains swallowed fluid and food. Consequently, the intravesophageal pressure in achalasia is raised, usually above atmospheric. Intraluminal pressures recorded after swallowing may be:
1. Simultaneous with maximum pressures up to 80 cm H$_2$O (Figure 10).
2. Multiple repetitive, gradually fading after three or four contractions (Figure 4b).
3. Feeble simultaneous contractions less than 20 cm H$_2$O.
4. No response at all.

It must be remembered that the oesophagus is always dilated and the recording units are measuring pressures in one common cavity. A rise in
Figures 2 to 10 are taken from Clinical Tests of Oesophageal Function, Earlam, R. J. (1976) and appear with kind permission of the publishers, Crosby, Lockwood, Staples (London).

REFERENCES