Achalasia of the Esophagus: *
Pathologic and Etiologic Considerations

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ACHALASIA of the esophagus is a disease of unknown cause which is characterized by disordered esophageal motility. Although many etiologic theories have been proposed, there is general agreement that it is a neuromuscular disorder. This concept has received support from pathologic studies of the esophagus which, from the time of their first description by Rake in 1926, have revealed a degeneration or absence of the esophageal myenteric ganglion cells. This has not been a consistent finding, however, and some investigators have described ganglion cells in normal appearance and numbers in apparently bona fide cases of this disease.[13, 30] These conflicting findings raise the question whether the changes in the myenteric ganglion cells are primary or secondary. To further cloud the picture, lesions of the vagus nerve fasciculi and of the vagal dorsal motor nucleus have been reported in achalasia patients.[20, 22]

The purpose of this study was to reinvestigate the pathologic features of achalasia in an effort to clarify some of the conflicting reports in the literature and to contribute, if possible, to knowledge of the cause of this disease.

Material and Methods

The material for this study was obtained from 34 patients with esophageal achalasia and from 59 control patients who died of other causes without evidence of esophageal disease. Ninety-six specimens of esophageal wall, 183 of vagus nerve, and three of brain stem were examined, and these form the basis of this report. The diagnosis of esophageal achalasia in nine necropsied patients was based on typical historical, esophagoscopic and roentgenologic findings. Esophageal motility studies showed the characteristic changes seen in this disease in all 25 patients from whom biopsy specimens were obtained at surgery.

Light Microscopy. Necropsy specimens of esophagus were examined in transverse sections at 2-cm. intervals from the squamocolumnar junction, which is here defined as the cardia, to the level of the cricoid in the case of the controls and throughout the length of the thoracic portion of the esophagus in the nine achalasia patients. Sections were stained with hematoxylin-eosin. Fifty control specimens and nine

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achalasia specimens were examined in this fashion for their general morphology, and counts were made of the number of ganglion cells seen in transverse section at the various levels.

Biopsy specimens of esophageal muscle of the lower 5 to 8 cm. of the esophagus were obtained in 25 patients with achalasia during modified Heller surgical procedures.[10] A longitudinal strip of esophageal muscle was excised from the lower portion of the esophagus throughout the length of the esophagomyotomy. Hematoxylin-eosin sections were prepared in 19 of these specimens and examined for ganglion cells. In all specimens, at least two ganglia were seen histologically.

One hundred twenty-seven specimens of vagus nerve obtained at necropsy from the 50 control patients at various levels of the esophagus from the cervical region to the cardia were studied in transverse section by means of hematoxylin-eosin, Mallory-Heidenhain,[15] Mallory phosphomolybdic acid hematoxylin,[24] Bodian and luxol fast blue staining procedures.[25] Thirty-nine specimens of vagus nerve obtained at necropsy and at thoracotomy from patients with achalasia were similarly studied.

Electron Microscopy. Additional muscle and vagus nerve biopsies in the area of esophagomyotomy in patients with achalasia were examined for abnormalities of fine structure. Ten muscle biopsies and nine vagus nerve biopsies from patients with achalasia were available for such studies. Eight muscle biopsies and eight nerve biopsies from patients undergoing thoracotomy for treatment of esophageal and pulmonary carcinoma and of duodenal ulcer (transthoracic vagotomy) were also obtained and used as controls. All materials were fixed in Dalton's solution,[7] dehydrated in graded-alcohol solutions and embedded in both butyl-methylmethacrylate (4:1) and Epon 812.[23] After sectioning and mounting, the material was examined with an RCA EMU-3E electron microscope.

Two brain stem specimens from patients with achalasia and one control brain stem obtained from a 72-year-old man who died as a result of myocardial infarction were serially sectioned transversely every 15 microns throughout the region of the dorsal motor nucleus of the vagus nerve. Ganglion cells were diminished in number or absent throughout the esophagus in these two cases of achalasia. The number of nerve cells constituting both the right and the left dorsal motor nucleus was counted for each section and tabulated. The numbers of cells in 50 section segments of the nucleus were then averaged and plotted graphically for each brain stem specimen.

Results

Light Microscopy—Esophagus. The light microscopic features of the normal esophagus are adequately described in standard textbooks. Several microscopic features seen in the necropsy material, however, deserve emphasis. Mononuclear cell infiltrates were commonly seen in the mucosa of the lower 4 to 6 cm. of the esophagus. In occasional cases, large numbers were seen within Auerbach's myenteric plexus. In the region of the cardia, the circular muscle layer occasionally appeared thickened relative to the longitudinal layer. Some authors have regarded this thickening as evidence of an anatomic lower esophageal sphincter.[4] The Auerbach myenteric plexus characteristically consisted of numerous ganglia interconnected with nerve fibers (Fig. 1a, b).

The esophageal wall was diffusely thickened in five of the nine necropsy specimens from achalasia patients. This was confined to the circular layer of the dilated segment. In three additional necropsy specimens, both the longitudinal and the circular layers of the dilated segment were unusually thin. In one specimen, the muscular layers of the dilated segment were normal.

Mucosal and submucosal infiltration with mononuclear cells was a prominent feature of the lower esophagus in achalasia nec-

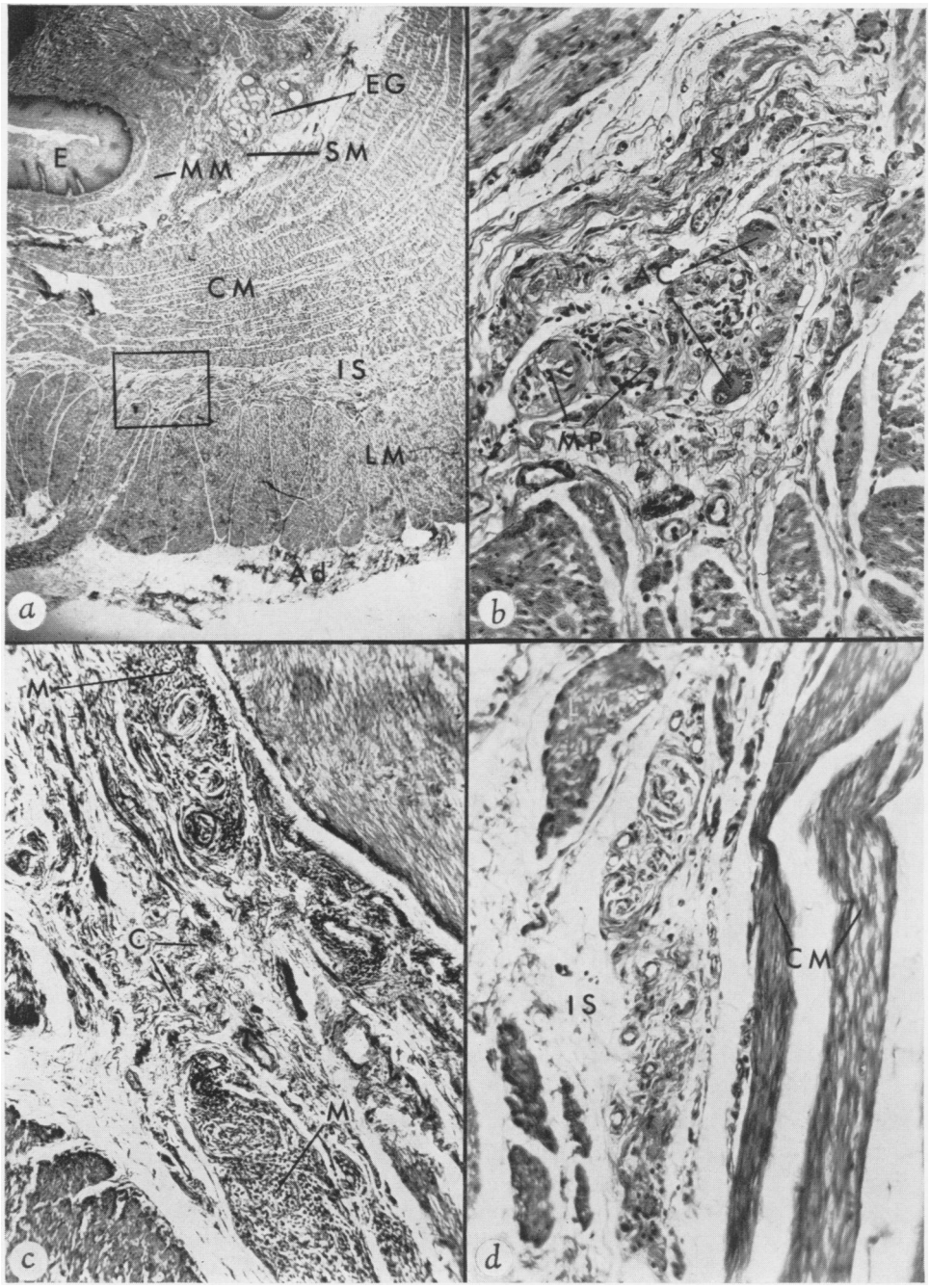

FIG. 1a. Normal esophagus. Low-power view of esophageal wall. Framed area is shown in higher magnification in 1*b*. Epithelium (E), muscularis mucosa (MM), submucosa (SM), esophageal glands (EG), circular muscle layer (CM), intermuscular septum (IS), longitudinal muscular layer (LM), and adventitia (Ad) are shown (hematoxylin and eosin; from × 15). b. Normal esophagus. Higher magnification of framed area shown in *a* showing myenteric plexus (MP). Auerbach cells (AC) have peripheral distribution in ganglion. Intermuscular septum (IS) (hematoxylin and eosin; from × 150). c. Esophagus in achalasia. Note absence of Auerbach cells with mononuclear infiltrates (M) into ganglia, plexus degeneration and mild increase in septal collagen (C) (from × 100). d. Esophagus in achalasia. Note absence of Auerbach cells without mononuclear cell infiltration into ganglion. Circular layer (CM), longitudinal layer (LM) and intermuscular septum (IS) are shown (from × 200).

ropsy specimens. This was often associated with focal areas of sclerosis. Mononuclear cells were found in myenteric ganglia associated with loss of ganglion cells (Fig. 1c); however, ganglia with loss of cells did not always show mononuclear cells (Fig. 1d). Adventitial or peri-esophageal changes in achalasia were commonly seen in necropsy material. These consisted of sclerotic changes about the esophageal nerves and adventitial vessels, which were otherwise normal in appearance.

The numbers of ganglion cells at various levels of the esophagus in necropsy specimens from control and achalasia patients are shown in Figure 2. Five pediatric patients were excluded from the control counts recorded in this figure. Ganglion cells were readily demonstrated at all levels of the normal esophagus except for the upper 6 cm. of the cervical portion of the esophagus. The ages of the patients ranged from infancy to 98 years and did not affect the cell counts as recorded.

In contrast, there was a marked reduction of ganglion cells in the dilated segment of the esophagus in seven of nine achalasia specimens. In the narrowed distal esophageal segment, ganglion cells were reduced in number by approximately 50 per cent. In two specimens, ganglion cells were normal in number and appearance throughout the dilated portion of the esophagus. One of these patients had had esophageal symptoms for only one year. The remaining patient had been symptomatic for 15 years with what was diagnosed clinically as cardiospasm, but radiologic evidence of esophageal dilatation was not present.

In addition to the necropsy studies, ganglion cells were also sought in biopsy specimens from 19 patients in whom the diagnosis of esophageal achalasia had been confirmed by esophageal motility studies. These findings have less validity, for in contrast to the necropsy specimens, only small segments of esophageal wall were available for study. As indicated in the table, ganglion cells were present in seven of the 19 patients.

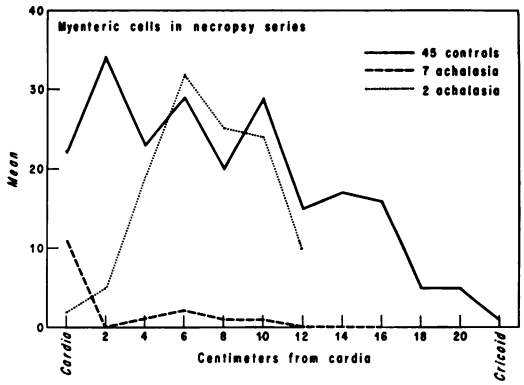

FIG. 2. Myenteric ganglion cell counts at various levels in esophageal necropsy specimens from control and achalasia patients.

Vagus Nerve. The normal cervical vagus nerve as seen under the microscope in transverse section is composed of several large fasciculi containing moderate numbers of myelinated fibers widely separated by large numbers of nonmyelinated fibers. Near the level of the aortic arch, the vagal trunk is partitioned into one or two large fasciculi resembling the cervical vagus nerve and into several heavily myelinated smaller fasciculi. The recurrent vagal nerves are usually composed of fasciculi with large numbers of myelinated fibers. Below the origin of the recurrent vagal nerves, the fasciculi of the vagus become smaller and contain progressively fewer myelinated fibers. The fasciculi of the vagal branches to the esophageal plexus are often totally nonmyelinated.

No major pathologic changes were noted in the light microscopic study of the vagus nerves at thoracic levels in patients with esophageal achalasia. The general composition and organization of the fasciculi also did not differ from control material.

Electron Microscopy. The fine structure of normal achalasic esophageal muscle and vagus nerve is described elsewhere in more detail [5, 6] and will be considered only briefly here.

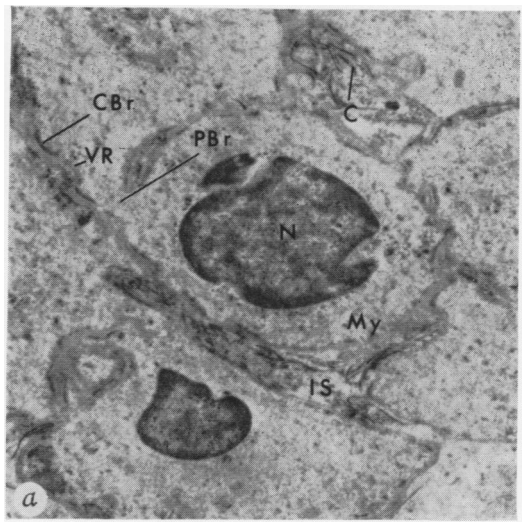

FIG. 3a. Normal esophageal smooth muscle. Transverse section. A sheet of smooth muscle cells showing complex bridges (CBr) with vesicular ridge (VR) in between, protoplasmic bridge (PBr) and centrally placed, indented nucleus (N). Myofilaments (My) are indistinct. Intercellular space (IS) contains collagen (C) and amorphous material (from × 10,000).

Esophageal Smooth Muscle. Normal muscle fibers were organized into continuous sheets of loosely arranged cells measuring 4.5 to 8.0 microns in width at their centers (Fig. 3a). Complex protoplasmic bridges were seen between the muscle cells. The bulk of the cytoplasm was made up of thin myofilaments which coursed longitudinally. A centrally placed nucleus and small numbers of cytoplasmic ribosomes and mitochondria were the major intracellular elements.

Three types of smooth muscle cell changes were noted in specimens obtained from patients with achalasia of the esophagus. The most prominent was the detachment of myofilaments from the surface membranes of the cells, a condition referred to as cellular autolysis[12] (Fig. 3b). Also noted was a reduction in caliber of the cells (cellular atrophy) with or without associated increases in cytoplasmic ribosomes (Fig. 3c). Occasionally, cells of increased caliber were found (cellular hypertrophy). The area of greatest change of each of the three types of smooth muscle cell change was localized to the junctional zone between the dilated and the distally narrowed segment of the esophagus. These changes were less marked in the area immediately above the junctional zone and least marked in the distally narrowed segment of the esophagus.

Esophageal Vagus Nerve. Normal vagal branches to the lower part of the esophagus contained predominantly nonmyelinated fibers ranging in size from 0.4 to 1.5 microns in diameter. Myelinated fibers were of small to medium caliber in the range of 1.5 to 6.6 microns. Cut transversely (Fig. 4a), nonmyelinated axons appeared as bright circular profiles placed within a darker layer of Schwann cytoplasm, and they maintained a communication with the Schwann cell surface by a double membrane structure, the mesaxon. Myelin fibers differed in that a dense myelin layer was situated between the axon and the Schwann layer. The axonic lumen contained a network of thin, branching neurofilaments ar-

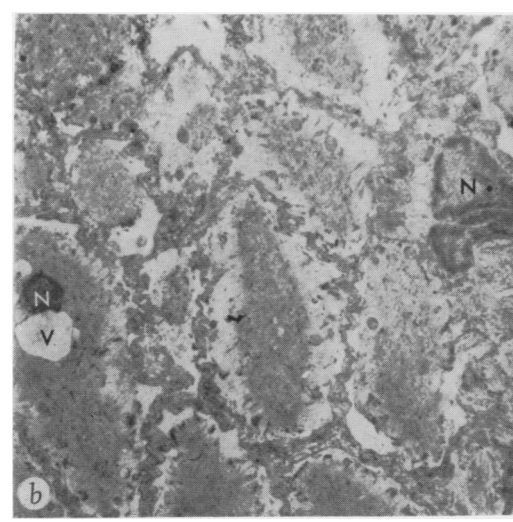

FIG. 3b. Esophageal smooth muscle in achalasia. Oblique section showing myofilament detachment involving groups of cells. Surface membranes are intact. Nucleus (N), vacuole (V) (from × 5240).

ranged longitudinally, in which were embedded mitochondria, ribosomes and endoplasmic reticulum.

Vagal branches to the lower portion of the esophagus in patients with achalasia featured morphologic changes similar to experimentally produced wallerian degeneration. Degenerated myelin appeared isolated into discrete masses (Fig. 4b). Decoiling of the myelin layer was seen in some myelinated axons. Axoplasm protruded into the myelin layer in others.

The most prominent morphologic alteration in nonmyelinated axons was a break in the continuity of the axon-Schwann membranes and of the mesaxons (Fig. 4b); this was associated with swelling of the axonic lumen and destruction of neurofilaments. In other nonmyelinated axons, the neurofilaments were fragmented and the axonic lumen was condensed (Fig. 4c). Several axons contained large numbers of degenerated mitochondria within their axoplasm. Schwann cells contained coarsely granular or relatively agranular cytoplasm, changes which suggested increased metabolic activity and degeneration, respectively. These

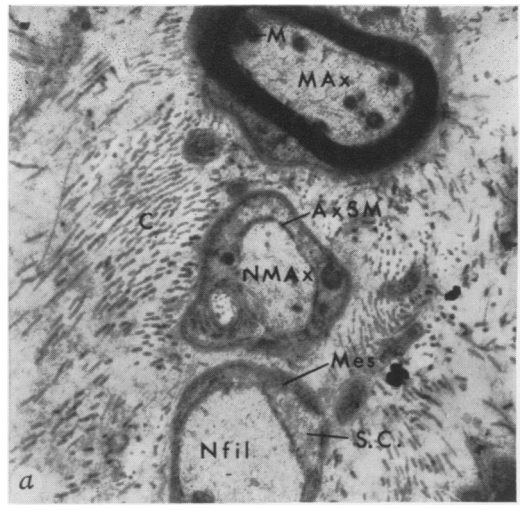

FIG. 4a. Normal esophageal nerve. Transverse section through myelinated and two nonmyelinated fibers. Axons of nonmyelinated fibers (NMAx) and myelinated fibers (MAx) are bright compared with Schwann cytoplasm (SC). Fibers are connected to surface of Schwann cells by mesaxons (Mes). Interstitial space contains collagen (C) and amorphous material. Neurofilament (Nfil), mitochondria (M) (from × 15,600).

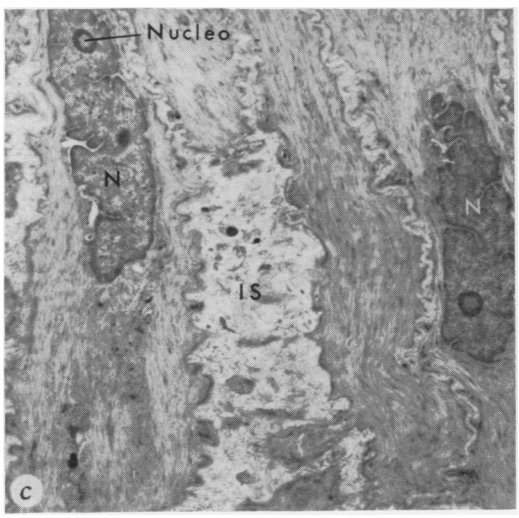

FIG. 3c. Esophageal smooth muscle in achalasia. Longitudinal section. Cells have decreased transnuclear caliber. Nucleus (N), nucleolus (Nucleo), interspace (IS) (from × 4370).

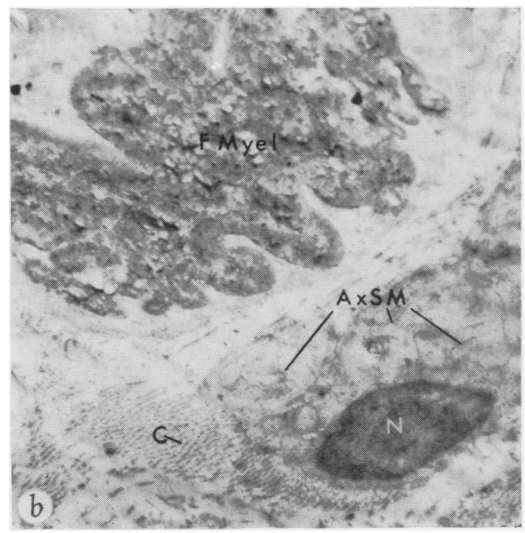

FIG. 4b. Esophageal nerve in achalasia. Folded myelin lamella (FMyel) forms isolated masses. Schwann cell contains disrupted axon-Schwann membranes (AxSM) and confluent axon and Schwann cell cytoplasms. Nucleus (N), collagen (C) (from × 9790).

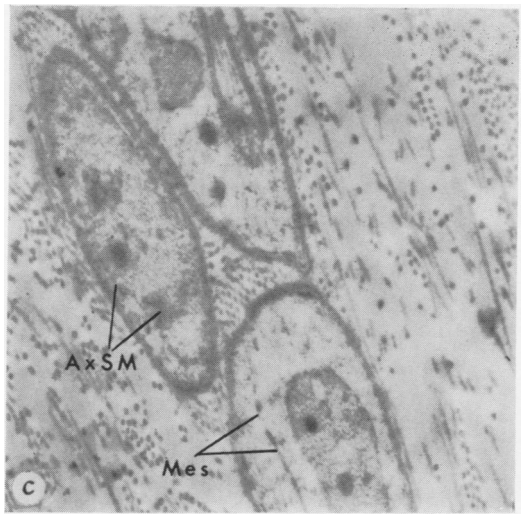

FIG. 4c. Esophageal nerve in achalasia. Oblique sections through three nonmyelinated fibers. Axons contain fragmented and condensed neurofilaments with degenerated mitochondria. Surrounding Schwann cytoplasm has little particulate material. Mesaxon (Mes) is fragmented as shown. Axon-Schwann membranes (AxSM) (from × 25,000).

changes were never seen in the control specimens.

Brain Stem. The normal dorsal motor nucleus of the vagus nerve extended from the olive cranially to the junction of the medulla spinalis and oblongata inferiorly. The approximate nuclear length was 15 mm. Two types of cells were seen within the nucleus. The majority at all levels of the nucleus were the elongated or pear-shaped dorsal motor cells, which measured between 19 and 29 microns. Cells of a second type were found in small numbers; these were tadpole-shaped and measured between 12 and 17 microns. The function of cells of the second type is uncertain.

In the control specimen, cranially, 30 to 60 dorsal motor cells were seen in transverse section through the dorsal motor nucleus bilaterally (Fig. 5a) while cau-

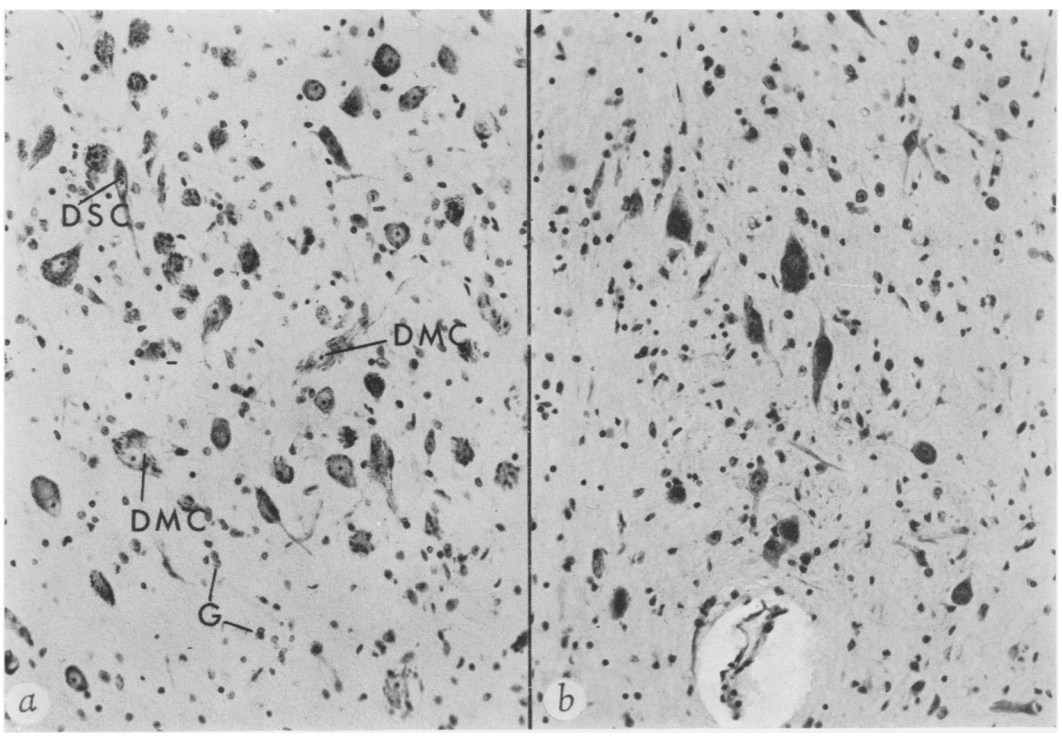

FIG. 5. Dorsal motor nucleus of the vagus nerve. a. Normal appearance of cranial portion of nucleus. Dorsal motor nuclear cells (DMC) contain coarse Nissl granules and are larger than dorsal sensory cells (DSC), which are tadpole-shaped and contain fine or indistinct Nissl granules. Glia (G) (× 200). b. Appearance of cranial portion of nucleus in patient with esophageal achalasia. Dorsal motor cells are cytologically distorted. Number of dorsal motor nuclear cells is markedly reduced (× 200).

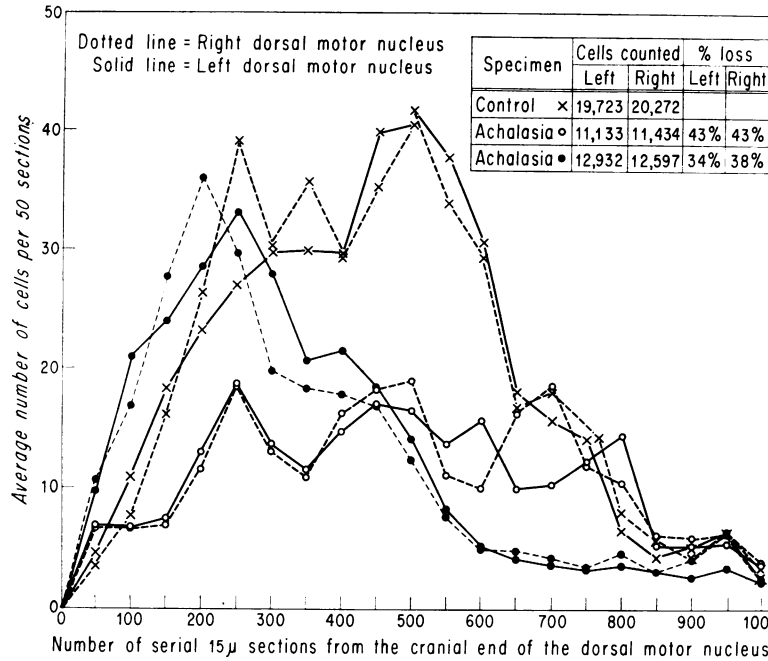

FIG. 6. Dorsal motor nuclear cell counts in a patient who did not have esophageal disease compared with findings in two patients with achalasia of esophagus.

dally, less than ten cells were seen. The relative density of dorsal motor cells throughout the length of the dorsal motor nucleus is illustrated in Figure 6. The total numbers of cells counted, however, were in excess of the actual number of cells present, since the average size of the dorsal motor cells was 26 microns and sections were 15 microns in thickness; this resulted in some double counting but ensured that no cells were uncounted.

Many of the dorsal motor cells of the vagal nucleus in two patients with achalasia of the esophagus were cytologically distorted. Fragmentation and dissolution of nuclear material and of Nissl granules were commonly seen, but these could not be distinguished with certainty from postmortem changes (Fig. 5b). Both patients were found to have a markedly reduced number of dorsal motor nuclear cells bilaterally, amounting to 43 per cent bilaterally in one patient and to 34 per cent on one side and 38 per cent on the other in the other patient (Fig. 6). It must be emphasized that a direct comparison of cell numbers at specific levels of the dorsal motor nucleus in the three brain stem specimens as illustrated in Figure 6 cannot validly be made, since no attempt was made to match specific levels of each brain stem anatomically with the other; rather, the graphic illustrations of the three brain stem specimens have been grouped as a matter of convenience.

Comment

For a proper understanding of the implications of these findings, a brief review of current concepts regarding the innervation of the esophagus is helpful. The vagus nerve contains both afferent and efferent, or sensory and motor, fibers (Fig. 7). Sensory receptors have been described in both the mucosa and the muscularis throughout the human esophagus.[28] These receptors are presumably the end organs of sensory fibers which arise from cells in the nodose ganglion of the vagus nerve in man [17] and the rhesus monkey.[18] It is established that efferent fibers arise only from the dorsal nucleus of the vagus in the

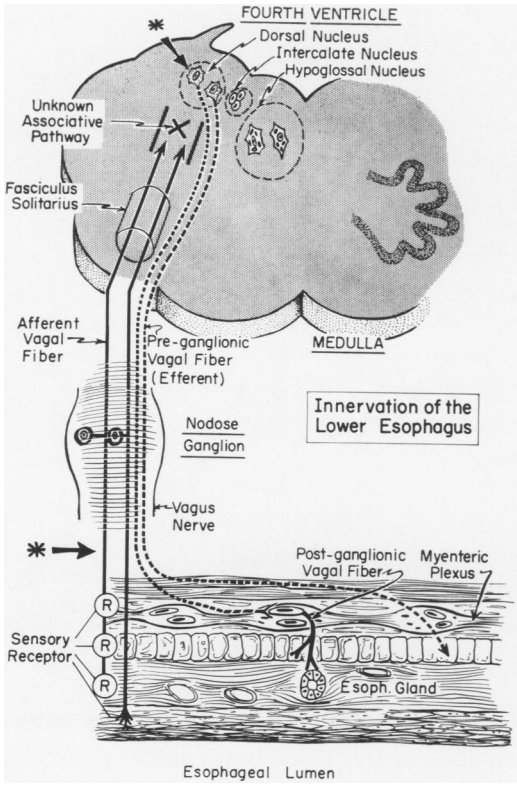

FIG. 7. Normal vagal innervation of lower esophagus. Asterisk indicates possible primary site of disease.

brain stem. Whether such fibers supply the entire length of the esophagus, innervating both smooth and striated muscle, has never been completely resolved. It is generally agreed that the sympathetic nerves contribute fibers to the vagus, but the total contribution to the vagus of man is considered small.[17] The thoracic portion of the esophagus is innervated by the esophageal plexus which surrounds the esophagus and gives off branches which penetrate the esophageal wall.

More complex and equally incompletely understood are the vagal connections with ganglion cells of Auerbach's plexus in the esophagus. However, the vagal efferent fibers are thought to enter the intramural ganglia and, probably, to make synaptic connections with some of the nerve cells whose postganglionic axons, in turn, activate large numbers of effector cells.[16] The interrelationship of groups of muscle cells and the integrity of individual cells are therefore of considerable importance for proper neuromuscular transmission in smooth muscle.

It is generally agreed that a disturbance in this neuromuscular mechanism is responsible for achalasia of the esophagus. The common finding of degeneration or absence of cells in Auerbach's plexus has been incriminated by many as the cause.[11, 21, 26] The current study has shown, as have others,[13, 30] that these changes are not necessarily seen in all cases of esophageal achalasia. Of a total of 28 specimens studied by light microscopy, only 19, or 68 per cent, had degeneration or absence of Auerbach's cells. In the majority of necropsy specimens of esophagus obtained from patients with achalasia, the greatest loss of myenteric cells occurred in the body of the esophagus, while in the narrowed distal segment, myenteric cells were usually found although in reduced numbers. Trounce and associates have also emphasized the fact that ganglion cells may be found in the distal narrowed esophageal segment of patients with this disease. It would appear, then, that achalasia of the esophagus is fundamentally different from congenital megacolon (Hirschsprung's disease), since in megacolon the narrowed segment is characterized by a decreased number or the absence of myenteric ganglion cells on histologic examination, relative to areas of colon immediately adjacent to it.[27]

Whereas changes in ganglion cells were inconstant in the material studied, evidence of lesions of the vagus nerve was found in each case when examined by electron microscopy. The appearance was that of wallerian degeneration. The degeneration of myelin sheaths, the disintegration of axoplasm, the presence of Schwann cells with coarse granules or no granules and the prominent endoplasmic reticulum are all features of degeneration seen experimen-

tally after nerve transection.[29, 31] It was not possible in the present study to determine the functional type or types of nerve axons undergoing degeneration, that is, whether they were sensory or motor, or both. Previous experimental studies in cats have shown that both motor and sensory axons in vagal branches to the esophageal plexus have myelinated as well as nonmyelinated components.[1, 8] In man, most vagal fibers at the level of the esophageal plexus are reportedly afferent.[17]

As far as we have been able to determine, no previous studies of the fine structure of the vagus nerve in achalasia have been reported, and light microscopic descriptions are rare. Normal findings have usually been reported in achalasia patients.[11, 21] Baudin, however, reported a case (previously described by Kelling, in 1903) of involvement of the vagus nerves by an inflammatory process in a patient with longstanding esophageal dilatation of a *functional nature*, while Loeper and Forestier (1921) described sclerotic and inflammatory lesions of the vagus in patients with cardiospasm associated with gastric ulcer or gastric carcinoma. Our studies of the esophageal nerves in achalasia do not suggest that an inflammatory or fibrotic process occurs in these nerves. When examined with the light microscope, the thoracic vagal branches could not be distinguished from controls.

The changes in the fine structure of esophageal smooth muscle in achalasia which we have described have also been reported by Harman and associates. We have made the additional observations of changes in cellular size, myofilament detachment and cellular ribosomal activity. Although the significance of these cellular changes is unknown, Franzini and Pellegrino have shown recently by electron microscopy that skeletal muscle in the rat undergoes both autolytic and atrophic changes at the cellular level after denervation which resembles the smooth muscle changes seen in the achalasia patients we have studied. The changes may, therefore, represent the picture of denervation atrophy.

Studies of the central nervous system in achalasia of the esophagus have previously been reported only by Kimura. His findings in two necropsy cases established the presence of bilateral degenerative vagal nuclear changes in both specimens of brain stem studied. Because of the difficulty in judging the significance of the various cytologic changes in neurons of the central nervous system that have been reported, the present study was concerned primarily with the relative numbers of cells present in the dorsal motor nuclei of the vagus in patients with achalasia. The pronounced bilateral reduction in the numbers of cells in the dorsal motor nuclei in two patients reported herein supports the earlier findings of Kimura as to the presence of significant central lesions in patients with achalasia.

In summary, then, we have encountered the following pathologic abnormalities in patients with esophageal achalasia: evidence of vagus nerve injury resembling wallerian degeneration, reduction in the number of cells in the dorsal motor nucleus of the vagus nerve, esophageal smooth muscle denervation atrophy and degeneration or absence of Auerbach cells in most, but not all, of the patients studied. It seems to us that these findings are consistent with the theory that the primary site of involvement in esophageal achalasia is not in the esophagus itself but in the extrinsic neural structures, that is, either the dorsal motor nuclei of the vagus or the peripheral vagus nerve trunk itself. The morphologic alterations in the esophageal myenteric cells and muscular layers are considered to result secondarily from a progressive extra-esophageal denervation process of long duration. The inconsistent changes in the ganglion cells could well be a reflection of the fact that

TABLE 1. *Achalasia of the Esophagus: Clinical and Pathologic Correlation*

Duration of Symptoms	No. of Cases	Ganglion Cells		Motility Disturbance			Esophageal Dilatation		
		Present	Absent	Mild	Moderate	Marked	Mild	Moderate	Marked
<10 years	14	7	7	3	10	1	5	8	1
>10 years	5	0	5	0	1	4	2	1	2
Total	19	7	12	3	11	5	7	9	3

trans-synaptic cell degeneration requires considerable time to develop, as demonstrated experimentally in the sympathetic nervous system by Dumont and associates.

If such a theory is correct, there should be clinical evidence to support it. Such evidence was sought in 19 patients with esophageal achalasia proved by esophageal motility studies in whom specimens of esophageal muscle were available for pathologic examination and esophageal roentgenograms for review. In all cases it was possible to date accurately the onset of the patient's symptoms. The findings are summarized in Table 1.

Ganglion cells were found on examination of the esophageal biopsy specimens in 50 per cent of the patients who had been symptomatic for ten years or less, whereas they were absent in all patients who had been symptomatic for more than ten years.

The esophageal motility pattern was designated as mild, moderate, or marked, depending on the amplitude of the nonperistaltic deglutitive contractions of the lower part of the esophagus.* Thus, if the esophagus was essentially paralyzed without significant response to deglutition, the motility disturbance was classified as *marked.* When feeble contractions were recorded in response to swallowing, the disturbance was considered *moderate,* while the classification *mild* was given to those patients whose nonperistaltic deglutitive contractions were of normal amplitude or only slightly reduced. Patients with dysphagia for ten years or less had motility patterns of mild or moderate achalasia for the most part. In contrast, the motility pattern was marked in four of the five who had had symptoms of more than ten years' duration. These changes in esophageal motility correlated better with the changes in the ganglion cells and with the duration of the patient's disease than they did with the degree of esophageal dilatation as demonstrated radiographically. In addition, they are in keeping with the theory that the primary site of the disease is in the nerve pathways extrinsic to the esophagus and that, with the passage of time, this disorder leads to progressive loss of myenteric cells and progressive paralysis of the thoracic portion of the esophagus above its inferior sphincter.

If this concept is correct, other evidence of vagal nerve dysfunction should be sought in patients with esophageal achalasia. As far as we know, this has not been done on any large scale. However, Iordanskaia, using the Hollander test in studying 32 patients with esophageal achalasia, found marked alteration or entire ablation of vagal function in some. These findings suggest the possibility of abnormal motor innervation to the gastric parietal cells in some patients with this disease.

Summary

A pathologic study of the esophageal wall, vagus nerve and dorsal motor nu-

* We are grateful to Dr. C. F. Code for his help in analyzing these records, all of which were prepared in his laboratory.

cleus of the vagus nerve was undertaken. Specimens from 34 patients with esophageal achalasia and 59 control patients without esophageal disease form the basis of this report. Degeneration or absence of myenteric ganglion cells was noted histologically in 68 per cent of cases and correlated well with the duration of the patient's symptoms. In seven of nine necropsy specimens, the most marked cell losses were encountered in the dilated segment; cells were present in the narrowed distal segment of the esophagus though reduced in number by approximately 50 per cent.

The thoracic portion of the vagus nerve in patients with achalasia was indistinguishable from control specimens by light microscopy; however, with the electron microscope, changes resembling experimental wallerian degeneration were always seen. When studied with the electron microscope, esophageal smooth muscle in achalasia showed three principal types of cellular change consistent with denervation atrophy: myofilament detachment from surface membranes, cellular atrophy and, uncommonly, cellular hypertrophy.

Cell counts of the dorsal motor nucleus of the vagus nerve in two patients with esophageal achalasia revealed losses of 43 per cent of dorsal motor cells bilaterally in one patient and of 34 per cent on one side and 38 per cent on the other in the second patient as compared with a control specimen.

It is suggested that an extra-esophageal vagal lesion, either of the peripheral vagus nerve or of its dorsal motor nucleus, is the primary site of involvement in esophageal achalasia and that the esophageal changes are secondary.

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Discussion

Dr. K. Alvin Merendino (Seattle): Dr. Ellis suggested at one time that I might be interested in seeing this paper and perhaps discussing it. I have not had the opportunity of seeing it, but I arise to congratulate the authors on what I think is one of the finest recent studies on cardiospasm that I have heard.

There are few things that I can say. Their data suggests that perhaps there may be a neurogenic aspect of this disease which is more central than most of the studies which have been accomplished in the past. All of us are familiar with the fact that often the onset of the cardiospasm follows a sudden emotional disturbance in individuals often emotionally unstable. This implies that there may indeed be central neurogenic lesions which we have not been able to identify previously.

Dr. Keith Grimson (Durham, North Carolina): Degenerative changes of nerve branches and changes or absence of cells of the myenteric ganglia well may explain dysphaglia related to failure of peristalsis of the lower esophagus. Complete absence of ganglia may not be necessary.

Three observations will be presented, one demonstrating relief of the physiologic obstruction, the other two questioning any role by the extrinsic nerves. As you know, a large esophagocardioplasty was a popular operation some years ago. The first observation is that with adequate drainage, the greatly enlarged esophagus of achalasis usually does gradually decrease to a normal size during a year or two of observation. In 12 patients, relief of obstruction allowed return of the esophagus to normal size, but reflux esophagitic occurred in six. The remaining six had a less complete drainage with persistence of some dilatation, but with less severe esophagitis.

This esophagitis can be corrected by vagotomy with gastro-enteropathy, or the wide cardioplasty can be performed initially along with vagotomy and a drainage procedure. My point is that relief of obstruction caused by dysfunction of the lower