

Oesophageal sensitivity to Mecholyl in symptomatic diffuse spasm¹

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EDITORIAL COMMENT Hypersensitivity to Mecholyl has been demonstrated in a number of patients with diffuse oesophageal spasm and this suggests that it is related to achalasia.

During radiographic examinations of the oesophagus, particularly in elderly individuals, a variety of bizarre contractions sometimes may be observed. These motor abnormalities are frequently incidental findings during routine gastrointestinal radiographs of patients for symptoms which are not oesophageal in origin. Occasionally the same contractions are seen in patients with odynophagia, dysphagia, and substernal pain and have been identified as responsible for such symptoms Moersch and Camp (1934). Because of their radiographic appearance, these motor disturbances have been variously called 'curling', 'tertiary contractions', 'segmental spasm', 'ladder spasm', 'non-sphincteric spasm', 'rosary-bead oesophagus', 'spastic pseudo-diverticulosis', 'corkscrew oesophagus', 'diffuse spasm'. Some authors have implied that different diseases are represented while others have stated that the changes are simply different radiographic manifestations of the same disorder. The latter view is the one that presently prevails (Templeton, 1964; Sheinmel, Priviteri, and Poppel, 1949; Van Exter and Keet, 1954; Creamer, Donoghue and Code, 1958).

Diffuse spasm (the term most commonly used), whether symptomatic or asymptomatic, is considered to be a neuromuscular disorder involving the body of the oesophagus whereas the sphincteric area usually functions normally (Creamer *et al.*, 1958). Cardiospasm also is a neuromuscular disorder but is said to differ pathologically and clinically in several important respects. Degeneration of Auerbach's plexus has been demonstrated in cardiospasm whereas no such lesion has been found in diffuse spasm (Templeton, 1964; Paden, 1954; Roth and

Fleshler, 1964). The cardiospastic oesophagus responds in a hypersensitive fashion to parasympathomimetic agents (Kramer and Ingelfinger, 1949; Kramer and Ingelfinger, 1951; Hightower, Olsen, and Moersch, 1954); in diffuse spasm no such response is said to occur (Creamer *et al.*, 1958; Johnstone, 1960). Patients with symptomatic diffuse spasm typically complain of pain, regurgitation is rare, and on radiological examination there are segmental spasms, relatively prompt oesophageal emptying, and little delay at the lower sphincter. In cardiospasm, pain is less common, regurgitation is frequent, the oesophagus seen in radiographs is often markedly dilated, emptying is greatly impaired, and the sphincteric area has a narrowed, tapered appearance.

In a preliminary communication we reported that the oesophagus in patients with symptomatic diffuse spasm manifested hypersensitivity to Mecholyl (Kramer, Fleshler and McNally, 1963). It was also suggested that diffuse spasm and cardiospasm are related disorders. The present paper is an extension of our previous study and a more detailed discussion of the findings in a larger number of patients with symptomatic diffuse spasm.

Two other groups of patients were investigated. One consisted of nine subjects (ages 56 to 72) with a similarly abnormal oesophagus radiologically but without oesophageal symptoms (asymptomatic diffuse spasm). The final group was composed of individuals over 50 years of age (the age of most diffuse spasm patients) with normal gullets radiologically and also without oesophageal symptoms.

Since this investigation is concerned primarily with the oesophageal response to Mecholyl, the phenomenon of oesophageal hypersensitivity to cholinergic agents needs to be defined. In cardiospasm this phenomenon had been characterized by

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a lumen-obliterating oesophageal contraction in response to a dose of Mecholyl which has little effect upon the normal oesophagus (Kramer and Ingelfinger, 1951). Theoretically the dose which separates the oesophagus which is hypersensitive from that which is not should be an amount just less than that which causes a lumen-obliterating contraction of the normal oesophagus. This dose has never been determined. In the previous study, the cardiospastic oesophagus was found to react with a tetanic contraction to 6 mg. or less of Mecholyl intramuscularly while 10 mg. had little effect in normal control subjects or in patients with a variety of oesophageal disorders. We have therefore considered 10 mg. or less of Mecholyl as the amount which determines oesophageal hypersensitivity. The average dose used is 6 mg.

METHODS

Oesophageal motility was investigated in every subject by fluoroscopy and x-ray film following barium swallows, and by balloon-kymography. In eight subjects with symptomatic and in two with asymptomatic diffuse spasm, intraluminal pressures were measured via water-filled polyvinyl catheters, Sanborn transducers, and a Sanborn recorder. Balloon-kymography and manometric measurements were performed by methods previously described (Kramer and Ingelfinger, 1949; Fleshler, Hendrix, Kramer, and Ingelfinger, 1958).

During balloon-kymography the balloon was placed

under fluoroscopy in the lower one-third of the oesophagus. After a suitable control tracing, an initial dose of 2 to 3 mg. of Mecholyl was injected intramuscularly. If a lumen-obliterating contraction was not obtained then increasing doses of Mecholyl were injected at 25-minute intervals, a larger dose consisting of an increment of 2 to 3 mg. of Mecholyl to the previous injection. This procedure was continued until at least 6 mg. was given or the typical hypersensitive response occurred. Tone was defined as the mean volume of air in the balloon in millilitres. The regularity of the wave pattern was determined by inspection. The number of waves per minute was counted from a representative portion of the control tracing. If the wave pattern was irregular, then the contractions per minute were not counted.

RESULTS

The results are set out in Table I.

SYMPTOMATIC DIFFUSE SPASM (14 PATIENTS) All the varieties of bizarre contractions implied by the synonyms commonly used were visualized radiologically (Fig. 1). Three types of motility pattern were observed by balloon-kymography (Fig. 2): 1 In six patients (Fig. 2a and b) the tone was normal (average 15 ml., range 11 to 23 ml.) and the waves occurred in regular sequence. However, the number of waves per minute (average 14 per minute, range 10 to 22 per minute) exceeded that

TABLE I

SUMMARY OF CLINICAL, BALLOON-KYMOGRAPHIC, AND MANOMETRIC DATA IN PATIENTS WITH DIFFUSE SPASM

Subject	Sex	Age	Balloon-kymography		Mecholyl Effect		Manometry	
			Tone	Wave Pattern	Response	Dose (mg.)	Motility	Sphincter Opening
<i>Symptomatic Diffuse Spasm</i>								
1 R.B.	F	58	Normal	Regular	Pos.	3		
2 F.C.	M	61	Normal	Regular	Pos.	3	D.S.	Yes
3 J.S.	F	63	Normal	Regular	Pos.	2		
4 M.C.	F	48	Normal	Regular	Pos.	6	D.S.	Yes
5 J.F.	M	58	Normal	Regular	Pos.	6	D.S.	Not tested
6 A.G.	M	73	Normal	Regular	Neg.	12	D.S.	Yes
7 C.P.	M	68	High	Irregular	Pos.	6		
8 Ja.S.	M	63	High	Irregular	Pos.	6	D.S.	Not tested
9 C.M.	F	48	High	Irregular	Neg.	10		
10 J.N.	M	68	Normal	Irregular	Pos.	5	D.S.	Yes
11 R.G.	F	48	Normal	Irregular	Pos.	4		
12 S.M.	M	72	Normal	Irregular	Pos.	3		
13 J.C.	M	63	Normal	Irregular	Neg.	10	D.S.	Yes
14 C.C.	F	38	Normal	Irregular	Pos.	6	D.S.	Yes
<i>Asymptomatic Diffuse Spasm</i>								
1 J.C.	F	68	Normal	Regular	Neg.	10	D.S.	Yes
2 B.M.	M	67	Normal	Regular	Neg.	6		
3 M.C.	F	70	Normal	Irregular	Neg.	6		
4 L.L.	M	63	Normal	Irregular	Neg.	10		
5 E.J.	F	68	Normal	Irregular	Neg.	6		
6 F.O.	F	72	Normal	Irregular	Neg.	6		
7 M.V.	F	68	Normal	Irregular	Neg.	6		
8 M.F.	M	56	Normal	Irregular	Neg.	10		
9 T.D.	F	72	Normal	Irregular	Neg.	10	D.S.	Yes

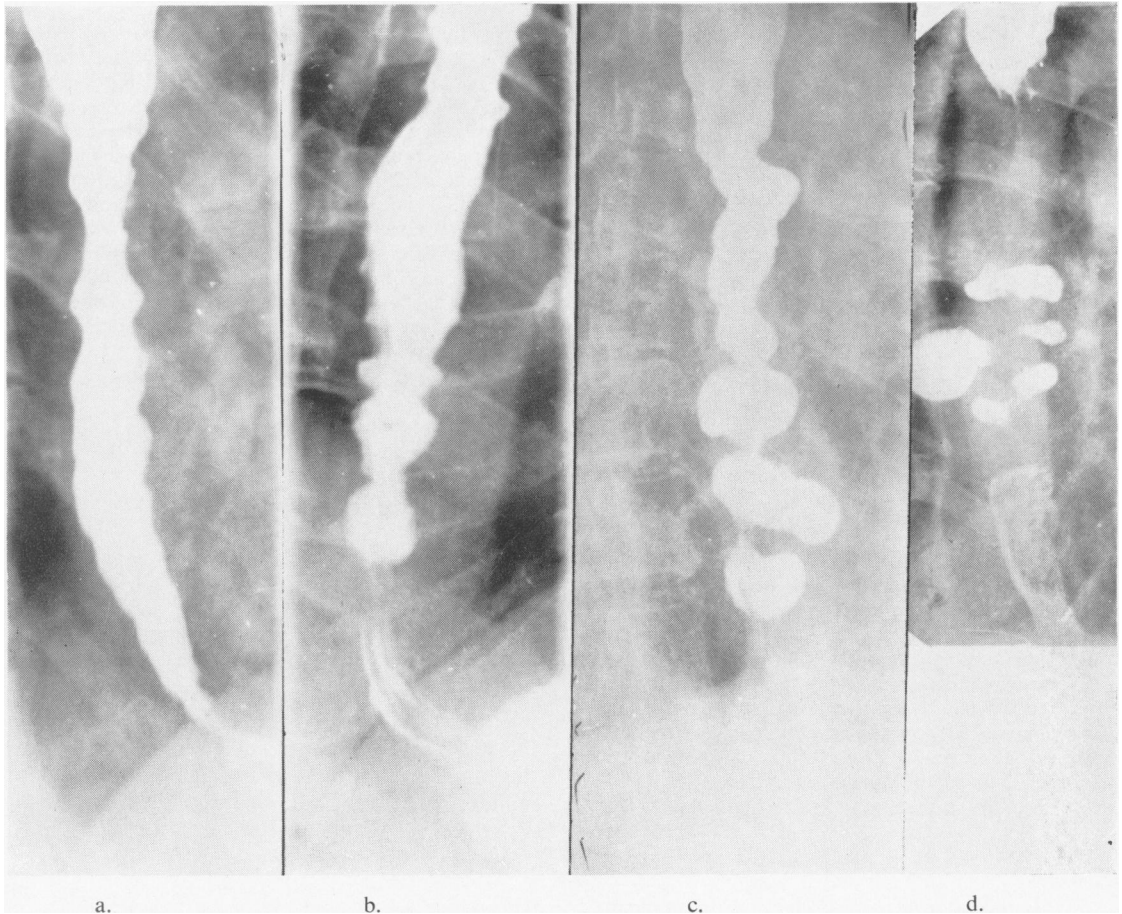


FIG. 1. Demonstrations of the gamut of oesophageal radiographic appearances in symptomatic diffuse spasm.

FIG. 1a (R.B.) Tertiary contractions or curling

FIG. 1b (F.C.) Segmental spasm

FIG. 1c (J.S.) Spastic pseudodiverticulosis

FIG. 1d (C.P.) Corkscrew oesophagus

usually seen in normals (average 8 per minute, range 6 to 12 per minute). 2 In three patients (Fig. 2d) the tone was unusually high (average 4.7 ml., range 3 to 8 ml.) and the wave pattern was difficult to discern. 3 In the five remaining patients the tone was normal (average 16 ml., range 10 to 25 ml.) but the wave pattern was irregular and could not be counted with any degree of accuracy (Fig. 2c).

The oesophageal response to Mecholyl by balloon-kymography was the significant finding. Eleven of 14 subjects responded to 2-6 mg. of Mecholyl with a forceful contraction expelling all air from the balloon (Fig. 2), an effect similar to that seen in cardiospasm (Fig. 3). Because of the high initial tone the response to Mecholyl did not look as dramatic as that usually seen in cardiospasm; the

response was unequivocal nevertheless. Four subjects experienced retrosternal pain at the time of the contraction, typical of the pain they felt clinically. The three patients who did not respond to Mecholyl were in no way different by radiography, balloon-kymography, and manometry from those who did.

Intraluminal pressures were measured at rest and during deglutition in eight of the 14 subjects (two with a negative Mecholyl test). In the body of the oesophagus, the normal peristaltic pressure waves were replaced on swallowing by exaggerated, repetitive and simultaneous contractions over a long segment typical of diffuse spasm (Fig. 4) as described by Creamer *et al.* (1958). Sphincteric opening, *i.e.*, a decrease in pressure of the high pressure zone during swallow, was determined in six subjects and observed in all six (Fig. 4).

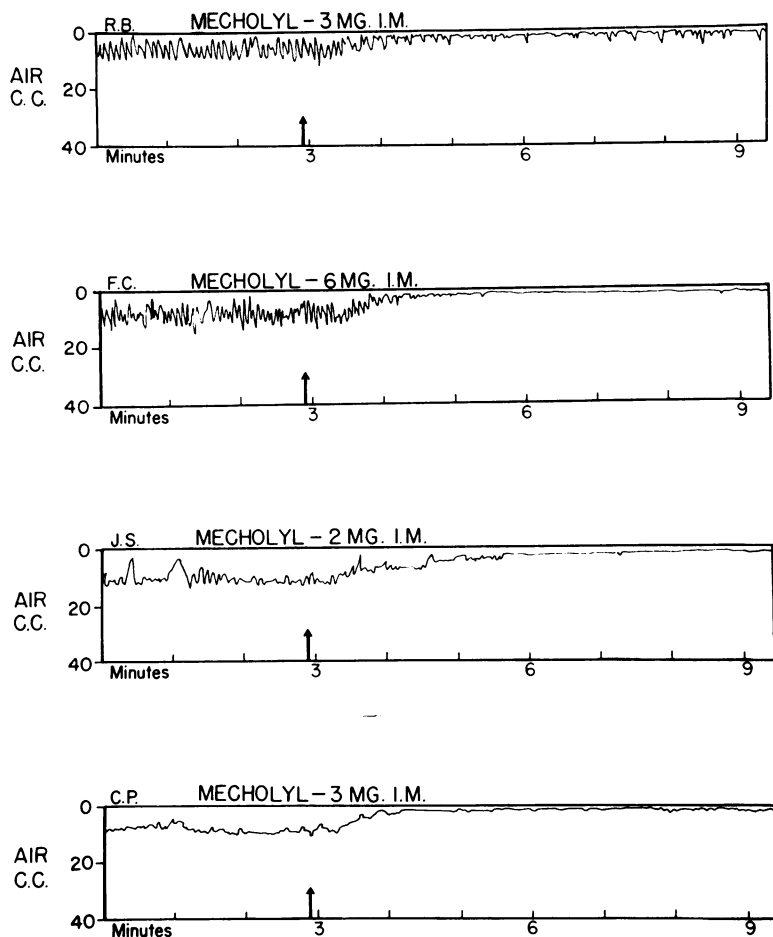


FIG. 2. Balloon-kymographic tracings of the four patients whose radiographs are seen in Figure 1. All show a hyper-sensitive response to Mecholyl.

ASYMPTOMATIC DIFFUSE SPASM (9 SUBJECTS) The oesophageal radiographs in these patients were similar to those seen in the symptomatic subjects (Fig. 5); none, however, showed the exaggerated appearance demonstrated in Figures 1c and d. Two types of balloon-kymographic motility pattern were obtained because of the character of the waves. The tone was normal in all tracings. In two subjects a regular wave pattern was seen with 11 and 8 contractions per minute. In the other seven subjects, the wave pattern was very irregular so that the number of waves could not be counted. Mecholyl in doses of 6 to 10 mg. intramuscularly produced minor alterations in motility similar to those seen in normals (Fig. 6). Manometric tracings, on swallowing, in two subjects were typical of diffuse spasm.

PATIENTS 50 YEARS OR OLDER WITH NORMAL MOTILITY BY X-RAY STUDIES (10 SUBJECTS) By balloon-

kymography, the average tone was 15 ml. The wave pattern was regular in seven subjects with an average of 7.8 waves per minute, and irregular in six subjects. Six to 10 mg. of Mecholyl intramuscularly produced slight minor changes in motility.

DISCUSSION

The validity of our findings depends upon whether or not our subjects had symptomatic diffuse spasm and not cardiospasm. Patients originally were selected because their symptoms and radiographic findings were typical of diffuse spasm.

In eight, the diagnosis was verified by the manometric tracings which were characteristic of diffuse spasm as they demonstrated exaggerated, repetitive, simultaneous, non-peristaltic contractions over a large area of the oesophagus with sphincteric openings in the six so tested. The radiographic

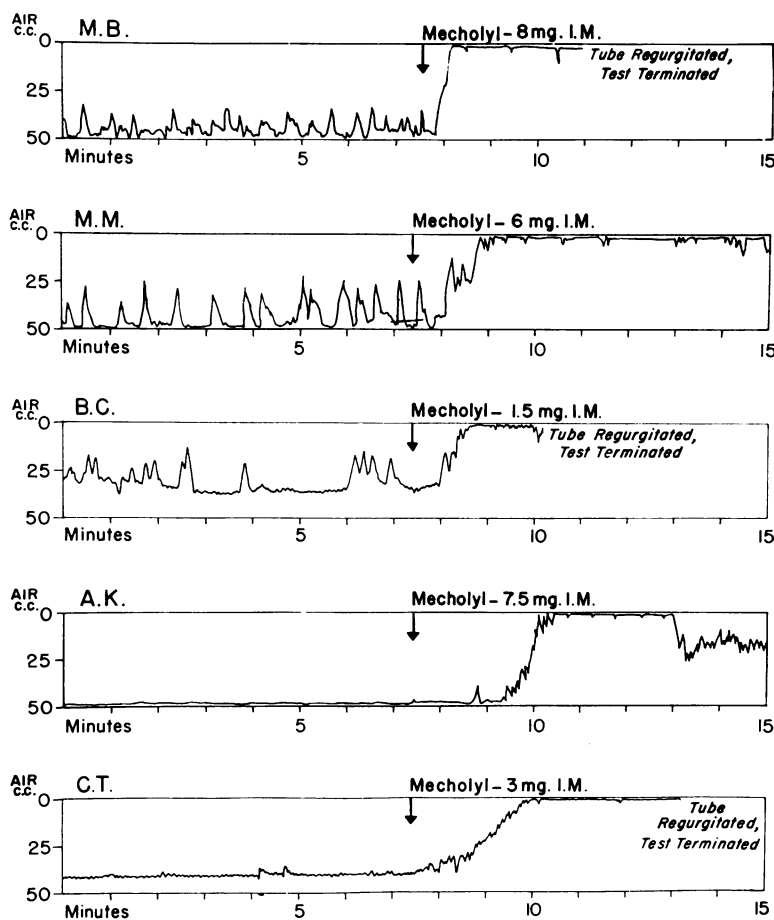


FIG. 3.

FIG. 3. Balloon-kymographic recordings in five patients with cardiospasm demonstrating the oesophageal hypersensitivity to Mecholy. (From Kramer, P., and Ingelfinger, F. J. *Esophageal Sensitivity to Mecholy in Cardiospasm*, 1951, *Gastroenterology*, 19, 242.)

FIG. 4. Manometric tracings from a normal oesophagus and from a patient, J.N., with symptomatic diffuse spasm. The three catheter tips are 6 cm. apart. The distal tip is in the sphincter. A line is drawn through the apex of the wave obtained via the proximal tip. D.S. denotes a dry swallow. In the normal, the middle wave occurs later than the proximal one indicating a peristaltic sequence. The tracing obtained via the distal catheter shows a high resting pressure (closed sphincter) and an 'opening pattern' on swallowing. In the patient with diffuse spasm the oesophageal contractions are simultaneous and repetitive but in the sphincteric area the high resting pressure and the 'opening pattern' is like that of the normal; however, the spasm often involves the sphincter as shown here.

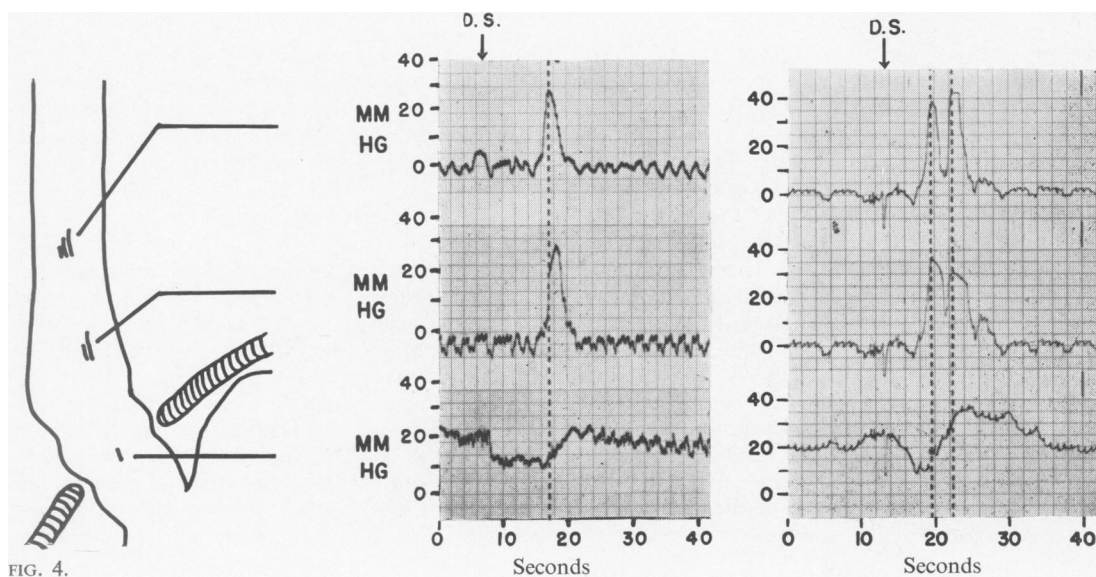


FIG. 4.

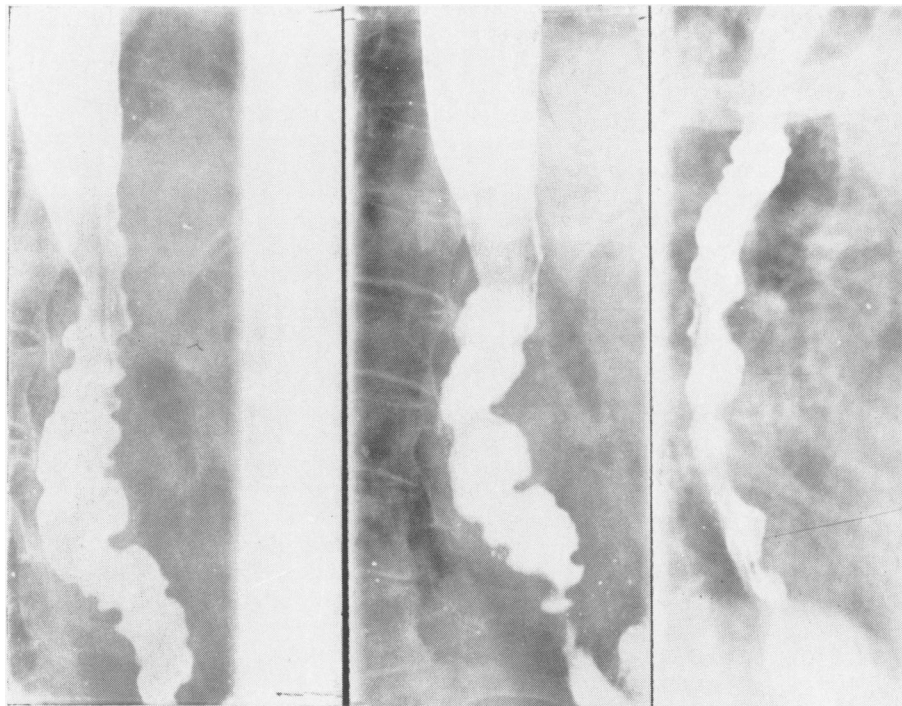


FIG. 5. The oesophageal radiographs seen in three asymptomatic individuals. These are representative of asymptomatic diffuse spasm.

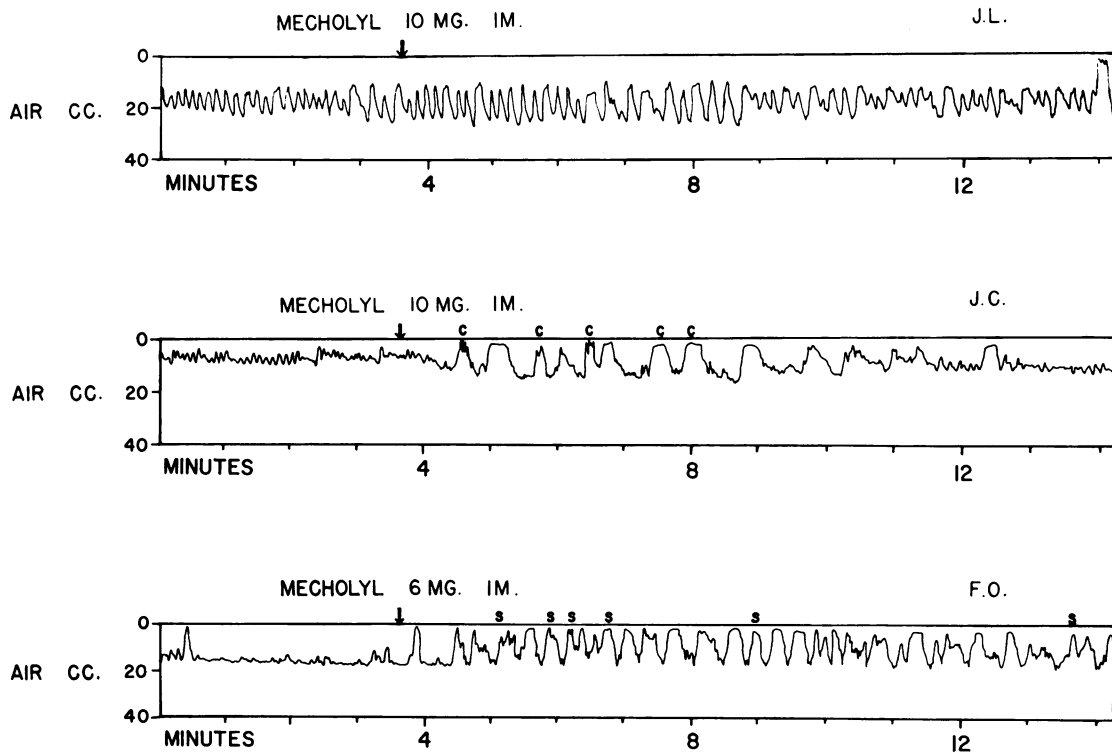


FIG. 6. Balloon-kymographic tracings of the patient whose radiographs are seen in Figure 5. The wave patterns before the injection of Mecholyl are similar to those seen in the normal. Mecholyl produces broadening of the waves but not a sustained lumen-obliterating contraction. C = cough; S = swallow. The end spike in J.L. is a calibration.

appearance of the oesophagi of patients J.S. and C.P. (Fig. 1c and d) could only be that of diffuse spasm. In the four remaining patients the *x*-ray findings, *i.e.*, the absence of dilatation, the failure to find a narrowed tapered distal area, and the ready oesophageal emptying, would argue against the diagnosis of cardiospasm.

Balloon-kymographic tracings in the three groups of patients investigated were not sufficiently different from one group to another to allow this technique to be particularly diagnostic. In three patients with symptomatic diffuse spasm the tone was unusually high and in six patients the number of waves per minute were increased above normal. However, even in elderly individuals without disease, all types of bizarre balloon-kymographic patterns can be observed (Kramer and Ingelfinger, 1951).

The crucial finding was the hypersensitive response of the oesophagus to Mecholyl by balloon-kymography in patients with symptomatic diffuse spasm, but not in the other two groups studied. This finding has three implications. First, it supports Templeton's and others' (Templeton, 1964; Creamer *et al.*, 1958) conclusion that the varied *x*-ray appearances in reality represent one clinical entity. Thus, the four representative patients in Figure 1, showing the gamut of abnormal contractions that can be visualized radiographically in symptomatic diffuse spasm, responded in a similar fashion to the cholinergic agent. Secondly, in cardiospasm the Mecholyl effect has been interpreted as pharmacological evidence confirming the pathological finding of antemortem degeneration of Auerbach's plexus according to Cannon's Law of Degeneration. Since the response in symptomatic diffuse spasm is similar, the possibility has to be considered that there is degeneration of Auerbach's plexus in this disorder. However, pathological studies, albeit few and incomplete, to date have not confirmed this speculation (Paden, 1954; Roth and Fleshler, 1964). Lastly, the similar response to parasympathomimetic drugs in symptomatic diffuse spasm and cardiospasm suggest that these two disorders may be related. Corroborative evidence is obtained by the findings in patient F.C. His symptoms, oesophageal radiographs, and motility studies were first suggestive of symptomatic diffuse spasm; later they were typical of cardiospasm. This patient is the subject of a separate report (Kramer, Harris, and Donaldson page 115).

Others (Creamer *et al.*, 1958; Johnstone, 1960) have reported a negative Mecholyl test in symptomatic diffuse spasm, yet we have presented evidence that it is frequently positive. The difference in results is probably related to the methods used in conducting the respective investigations. The pharmacological studies of Creamer *et al.* (1958) were

conducted with manometric techniques while we employed balloon-kymography. With the latter method, the large balloon separates the oesophageal walls, stretches them and acts as a constant stimulus thereby producing a continuous motility record. Consequently, when a muscle-stimulating drug such as Mecholyl is given, the oesophageal walls can readily react, especially when the muscle fibres are hypersensitive to the drug. Any changes which occur are readily discernible in the balloon-kymographic record.

On the other hand, with manometric techniques, the tiny balloon or open-tipped catheters are sufficiently small in diameter so that they do not separate the oesophageal walls nor induce motor activity. For intraluminal pressure to be recorded a force must be exerted over a unit area, *i.e.*, a cavity or lumen must exist and a closed chamber must be formed around the catheter ends. In the resting normal and diffuse spasm oesophagus the walls are in apposition. Since no lumen exists, no pressure rise can be registered when Mecholyl is given. However, the oesophageal muscle fibres may shorten and squeeze. Whether present methods used to detect pressure can record this squeeze is questionable (Harris and Pope, 1964). We strongly suspect that the positive Mecholyl response in cardiospasm by manometry is due in part to the fact that swallowed saliva, air, or ingested water, etc., are present within the oesophageal lumen in this disease because there is no peristalsis. These substances act like a balloon, stretch the oesophageal walls and permit the oesophagus to contract down when a cholinergic agent to which it is hypersensitive is injected. However, a closed chamber may not always form around the catheter tips and the pressure may be dissipated. In balloon-kymography, the balloon in fact is a closed chamber and a change in intra-oesophageal volume will be detected readily.

Can symptomatic diffuse spasm always be distinguished from cardiospasm? Typical cases of either disease produce no problem in diagnosis. However, atypical cases may lead to diagnostic difficulties. The clinical history may not be helpful since symptoms may overlap. Radiographic appearances may be somewhat similar since early cases of cardiospasm may show minimal dilatation and marked segmental contractions. Motility tracings with balloon-kymography lack specificity. The positive Mecholyl test in symptomatic diffuse spasm eliminates this procedure as a differential diagnostic tool. Peristalsis and sphincteric opening by manometric techniques are the major distinguishing findings in diffuse spasm; they are absent in cardiospasm. Unfortunately, approximately 25% of

patients with symptomatic diffuse spasm fail to show this opening pattern (Creamer *et al.*, 1958).

Many aspects of diffuse spasm remain an enigma. Why symptoms are present in some patients and not in others is unexplained; why the majority of patients with symptomatic diffuse spasm respond to Mecholyl in a hypersensitive fashion and others do not is also unknown; why the symptomatic group responds to cholinergic agents and the asymptomatic does not is also unanswered.

SUMMARY

Eleven of 14 patients with symptomatic diffuse spasm demonstrate an oesophageal hypersensitivity to Mecholyl by balloon-kymography. This finding suggests that (1) the varied radiographic appearances represent one disease, and (2) diffuse spasm and spasm may be related disorders.

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