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Role of Gastrin and Other Gastrointestinal Hormones in the Pathophysiology of Achalasia of the Esophagus

by

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Regarding the primary lesion of achalasia of the esophagus, the following few things, such as degenerative changes in the dorsal motor nucleus of the vagus nerve, lesion in the trunks of vagi, degeneration and/or disappearance of nerve cells in Auerbach's plexus of the lower esophagus and so forth have been observed. However, a clear understanding of the pathophysiology of this disease, for example adequate reason for abnormal high resting pressure of lower esophageal spincher (LES) in the patient with achalasia remains unsolved. Recently, Castell and Harris[12] reported that gastrin and other gastrointestinal hormones played a physiological role in the control of esophageal sphincter strength, and moreover, Cohen[15][16], et al. reported that these hormones were related to dysfunction of LES in patients with achalasia.

In this study, the author produced experimental achalasia in dogs with the injection of 5% phenol solution into the muscular layers of the esophagus according to Delover's method[18]. The effects of gastrin and other gastrointestinal hormones on achalasic sphincter were examined in these experimental dogs and clinical patients with achalasia.

Materials and Instruments

1) Dogs

Adult mongrel dogs of both sexes ranging in weight from 6 to 17kg were used.

i) Normal dogs

Thirteen dogs without phenol injection and nine dogs prior to phenol injection were used as controls.

ii) Dogs with achalasia-like lesion

According to Delover's method[18], 30 dogs were anesthetized with intravenous injection of Nembutal and their respiration was controlled with a respirator. The gastroesophageal junction (GEJ) was exposed transabdominally or transthoracically, and 5% phenol solution was injected into the muscular layer of the lower esophageal wall just above the diaphragma for the purpose of destroying the Auerbach's plexus.

Key words : achalasia, open tip method, lower esophageal sphincter pressure, gastrin, gastrointestinal hormone,

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A tuberculin needle was used in order to situate the injection between the outer longitudinal and the inner circular musculatures covering the esophagus as much as possible.

Nineteen dogs that survived more than one month after receiving phenol injections were used in this study. Although 30 dogs were injected with 5% phenol solution, 11 dogs died during the subsequent month because of esophageal perforation (5 dogs), emaciation due to dysphagia (3 dogs), pleurisy (2 dogs) and etc. (1 dog). The mortality rate was 36.7%. As the dogs could not swallow solid food immediately after phenol injection, they were given only milk and a fluid diet for a week postoperatively. The animals whose appetite was impaired intensely were maintained by receiving additional transfusions. Usually, after a week, phenol-injected dogs could swallow small solid food with but slight difficulty.

2) Clinical patients with achalasia

Seven patients with achalasia who were admitted to our surgical clinic were used.

3) Instruments for measurement of intraesophageal pressure

i) Polyethylene tube

The tube was constructed with an outer diameter of 2.0mm, an inner diameter of 1.0mm and a length of 200cm. The distal end of tube was sealed and the pressure sensitive tip was a side-opening, 1.0mm in diameter.

ii) Transducer (TOYO MEANS INC. Co. LTD.)

iii) Carrier Amplifier : RP-5 (NIHON KODEN Co. LTD.)

iv) Ink-writing recorder (NIHON KODEN Co. LTD.)

4) Gastrointestinal hormones and drugs

i) Tetragastrin (TEIKOKU ZOKI Co. LTD.)

ii) Secretin (The Boots Co. LTD.)

iii) Pancreozymin (The Boots Co. LTD.)

iv) Mecholyl (prepared in the Pharmacological Division, Yamaguchi University School of Medicine)

5) Gastrin-^{125}I-Kit (CEA-IRE-SORIN)

Methods

1) Measurement of intraluminal pressure of the esophagus

The open tipped method for measurement of intraluminal pressure established by CODE[17] and INGELFINGER[29] was used. POPE[49] reported that infusion of microliter quantities of fluid into the lumen of a closed sphincter allowed more accurate prediction of sphincter force of closure than does static measurement of intrasphincteric pressure. Recently many investigators[2)3)20)22)34)41)55)61] have used a constantly perfused recording system.

In this study the dogs were anesthetized with intravenous injections of Nembutal and were placed in a supine position. Respiration was controlled with a respirator. The

polyethylene tube was initially passed into the stomach and then slowly withdrawn across the lower esophageal high pressure zone up to the oral cavity. The resting intraluminal pressure was measured by the withdrawn method. The polyethylene tube was easily bent when passed into the stomach while it was difficult to fix the open tip in a constant position. Therefore, in this study the polyethylene tube was inserted into the gastric tube and both tubes passed into the stomach and then only the gastric tube was withdrawn, approximately 10cm, while the open tip of the polyethylene tube still remained in the stomach. The tube which was used for recording esophageal sphincter pressure was infused with distilled water at a constant rate of 15～16ml per 30min[2]. The proximal end of the polyethylene tube was connected to the pressure transducer and in turn to the multichannel recording system.

The transducer was fixed on the same horizontal line as that of the esophagus. Atmospheric pressure on the level of the esophagus used as the zero reference. Initially using 20 HZ filter of carrier amplifier, the measurement of intraluminal pressure was performed. Intraluminal pressure was influenced significantly by respiration and pulsation. In the gastroesophageal high pressure zone respiratory inversion point (RIP) was clearly observed in this procedure[44)53)]. After RIP was confirmed, finally mean (2 sec) filter was used because it was convenient for the measurement that influences of respiration and pulsation of the intraluminal pressure were reduced as much as possible (Fig. 1).

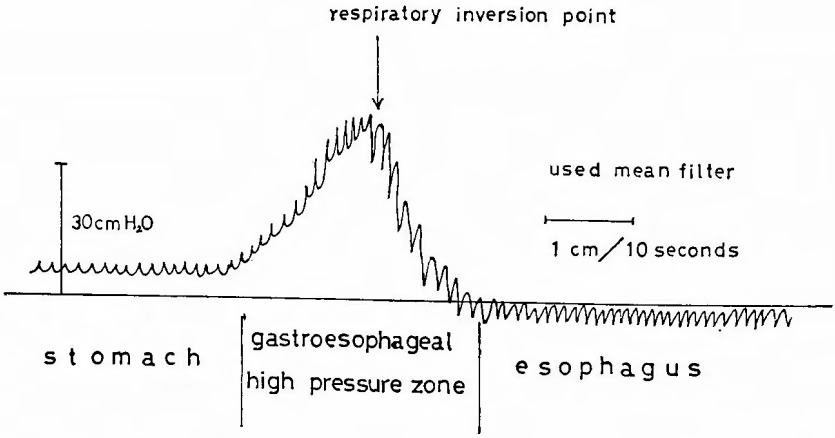

Fig. 1. Resting intraluminal pressure is recorded by withdrawn method. High pressure zone (HPZ) is detected as open tip crosses the gastroesophageal junction. Usually Respiratory Inversion Point (RIP) exsists in the HPZ.

i) Resting pressure at the gastoesophageal junction (GEJ)

Resting pressure was measured by the withdrawn method. The polyethylene tube was initially passed into the stomach and then slowly withdrawn at a constant speed of 1 cm per 10 seconds. Measurements of resting pressure at GEJ were performed on two groups. The first group consisted of 21 normal dogs while the

second group of 19 phenol-injected dogs.

ii) Lower esophageal sphincter (LES) pressure responses to Mecholyl and gastrointestinal hormones

The open tip was anchored in the position 1cm oral to RIP. After injection of Mechloyl or gastrointestinal hormones, LES pressure changed significantly and the position of open tip tended to move easily. Therefore, the gastric tube which was used as guide tube was fixed to a canine tooth to prevent the movement of the open tip. Changes of LES pressure responses to Mecholyl or gastrointestinal hormones were recorded continuously and finally LES pressure returned to the initial resting pressure. When LES pressure did not return to the initial resting pressure, movement of the open tip was doubted and thus the date were discarded.

2) Serum gastrin levels in dogs following Mecholyl injection

Five adult mongrel dogs were used. The dogs were kept fasting overnight and then anesthetized with an intravenous injection of Nembutal. The cutdown tube was cannulated into the inferior caval vein through the femoral vein in the dogs. Mecholyl was injected intramuscularly into each dog at a dose of 10mg. Blood samples were taken from the cannulated tube prior to the injection and also 30min. after the injection. The serum gastrin concentrations were determined by radioimmunoassay.

3) Histological examinations of the lower esophagus in phenol-injected dogs

All 19 dogs that survived more than one month after phenol injection were finally sacrificed. The parts of phenol-injected lower esophagus were resected and fixed with 10% neutral formaline. Histologic changes of the AUERBACH'S plexus were observed by the hematoxylin-eosin and the silver impregnation stains. The silver impregnation stain was performed using the modified BIRSHOVSKY's method. With this method the specimens were fixed in 10% neutral formaline for more than three weeks, later frozen and cut into slices 30-40μ in thickness.

Results

1) Production of experimental achalasia by phenol injection

The dogs that survived more than one month after phenol injection and normal dogs used for the following examinations.

a) Measurements of resting pressure at GEJ

In 19 phenol-injected dogs and 21 normal dogs the resting pressure at GEJ were measured by the withdrawn method. The mean resting pressure at GEJ was 38.1 ± 2.56 cmH_2O (mean ± 1 SE) in the phenol-injected group, while it was 20.6 ± 1.10cm H_2O in the normal group. The mean pressure in the phenol-injeted group was significantly higher than that in the normal group ($p<0.01$) (Fig. 2). Each resting pressure at GEJ in normal dogs was less than 30 cmH_2O. In 9 dogs, the pressure was measured before and after phenol injection. Six dogs showed higher pressure after phenol injection, but 3 dogs showed unchanged pressure.

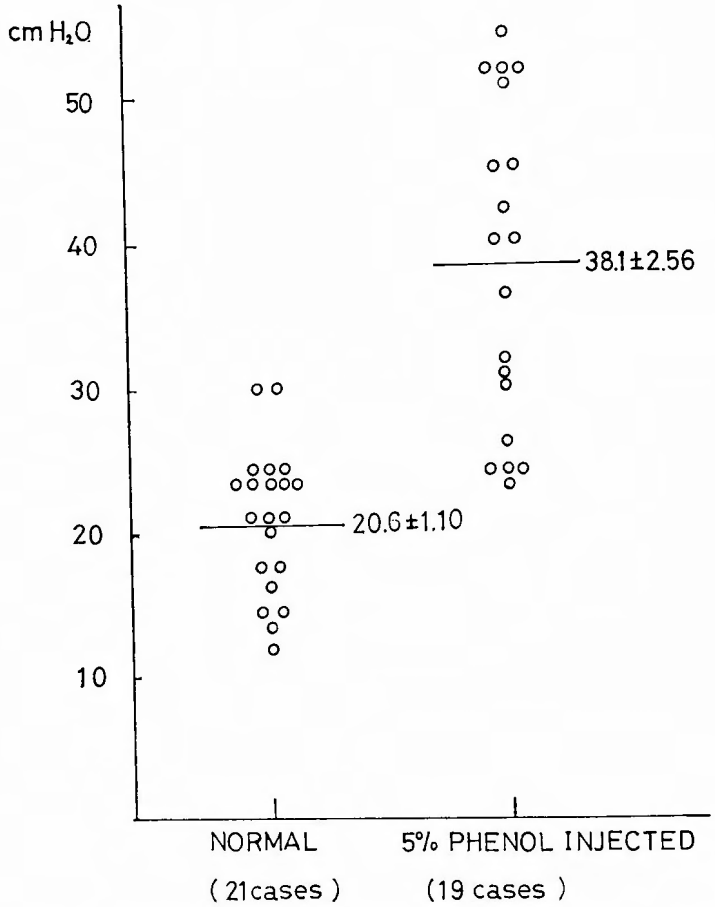

Fig. 2. Comparison of the pressures at gastroesophageal junction between normal and phenol-injected dogs
Mean pressure in normal dogs(21 Cases) is 20,6±1.10 cm H_2O(Mean±1 SE), while it is 38.1± 2.56 cmH_2O in phenol-injected dogs (19 Cases).

Table 1. LES pressure responses to intramuscular Mecholyl (5mg) injection

	normal dog			5% phenol-injected dog		
	resting pressure	peak pressure	difference	resting pressure	peak pressure	difference
	11	39	28	14	82	68
	6	40	34	7	90	83
	12	44	32	8	75	67
	8	27	19	10	90	80
	6	39	33	8	72	64
$\bar{X}$	8.6	37.8	29.3	9.4	81.8	72.4
1SE	1.24	2.85	2.75	1.13	3.66	3.80

$\bar{X}$=mean, unit=cmH_2O

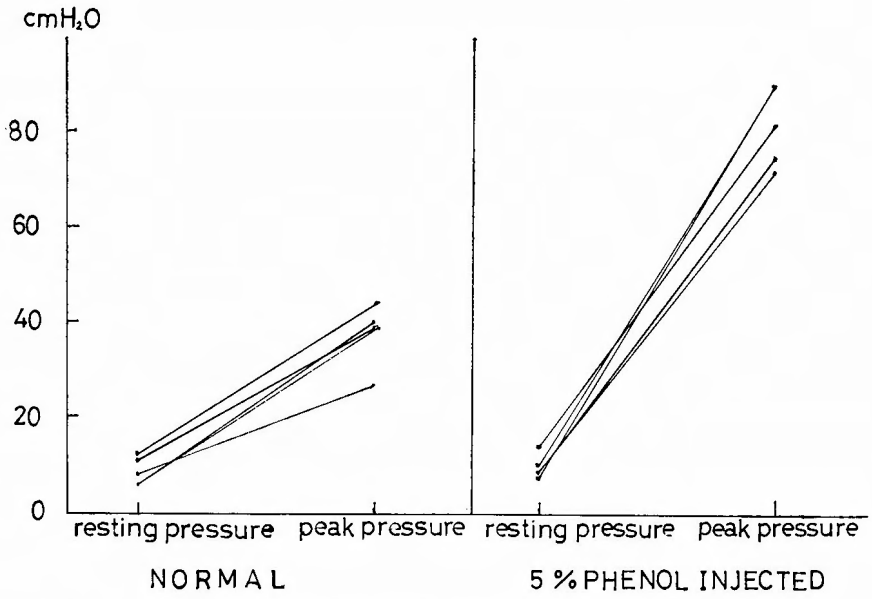

Fig. 3. LES pressure responses to intramuscular Mecholyl (5mg) injection in normal and phenol-injected dogs.
Increase in LES pressure is significant in phenol-injected dogs.

b) Mecholyl test

Experiments were performed on five phenol-injected dogs and five normal dogs (Tab. 1, Fig. 3). The open tip was anchored in the position 1cm oral to RIP and basal resting pressure was determined. Mecholyl at the dose of 5mg was injected intramuscularly into each dog. After Mecholyl injection, LES pressure increased within one minute, continued subsequently for 10～15min. and returned to the initial basal pressure. Peak-responded pressure was usually recorded 3～5min. after Mecholyl injection. After Mecholyl injection the LES pressure in normal dogs increased from a mean basal pressure of 8.6 ± 1.24 cmH_2O to a mean peak-responded pressure of 37.8 ± 2.58 cmH_2O, while the LES pressure in the phenol-injected dogs increased from 9.4 ± 1.36 cmH_2O to 81.8 ± 3.66 cmH_2O. The pressure difference between resting basal pressure and peak-responded pressure indicated 29.3 ± 2.75 cmH_2O in the normal group, while 72.4 ± 3.80 cmH_2O in the phenol-injected group. The comparison of increase in LES pressure responses to Mecholyl between normal and phenol-injected dogs showed a significant difference. The pressure difference was statistically great in phenol-injected dogs ($p<0.01$). This result agrees with the fact that LES in patients with achalasia shows hypersensitivity to Mecholyl[27]. In normal dog, resting pressure at GEJ ranged 23 cmH_2O, LES pressure increased from basal resting pressure of 6 cmH_2O to peak-responded pressure of 39 cmH_2O about 3 minutes after Mecholyl injection, while in phenol-injected dog, resting pressure at GEJ was 45 cmH_2O, LES pressure increased significantly from 8 cmH_2O to 72cm H_2O. The first pressure difference was 33 cm H_2O, while the last was 64 cmH_2O (Fig. 4).

Photo 1. Auerbach's plexus in normal dog, H.E. stain, Magn. 200

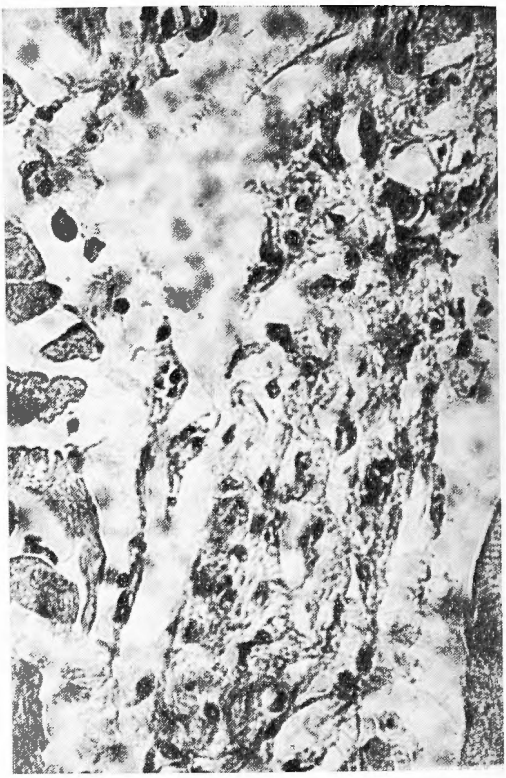

Photo 2. Auerbach's plexus in phenol-injected dog, H.E. stain, Magn. 200×

c) Histological examinations

i) Hematoxylin-eosin stain

① Normal dogs

There was a mass of nerve cells which had large cellular bodies and hyperchromic nuclei between external longitudinal and internal circular musculatures in the region of AUERBACH's plexus [8] (Photo 1).

② Phenol-injected dogs

The connective tissues increased remarkably and nerve cells almost disappeared in the region between longitudinal and circular musculatures in which AUERBACH's plexus was present in normal dogs. In other cases, intramuscular region became loose and retracted nerve cells appeared scatteringly[40)45)] (Photo. 2). When phenol was injected in a large dose into one portion, cell infiltrations and inflammatory changes involved the muscular layers and then muscular fibers were broken up[59)].

ii) Modified BIRSHOVSKY's stain

① Normal dogs

A mass of polymorphic nerve cells appeared in Auerbach's plexus in the lower esophagus. Each nerve cell usually contained one nucleus which located peripherally in the cellular body. Axon which was known as postganglionic nerve fiber appeared starting from the nerve cell[40)]. Nerve fiber, so-called dentrite, which kept connection

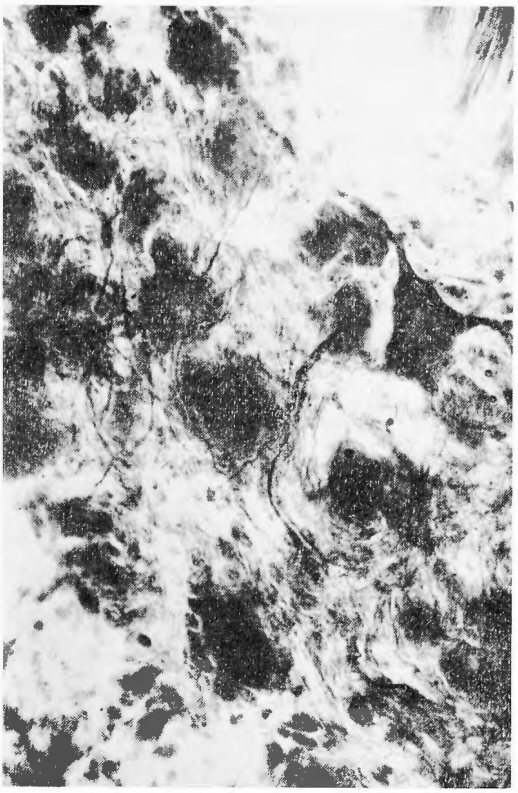

Photo 3. Nerve cells and fibers in normal Auerbach's plexus, Modified Birshovsky stain, Magn. 400

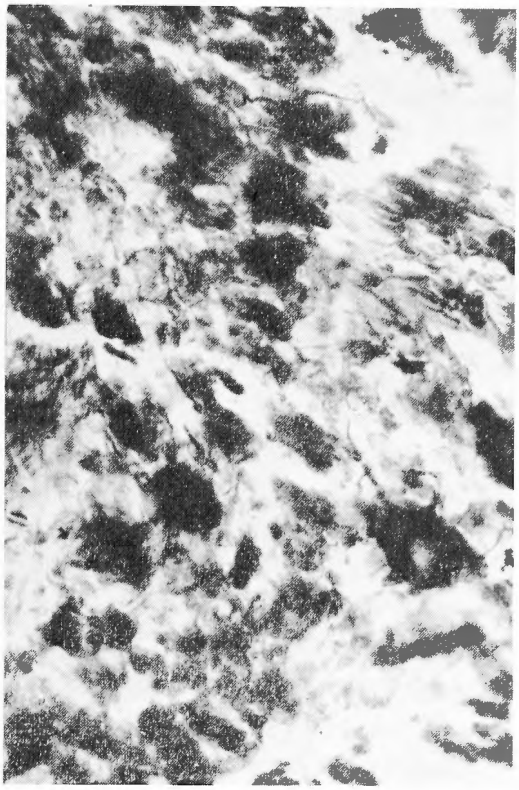

Photo 4. Degenerated nerve cells and fibers in phenol-injected Auerbach's plexus, Modified Birshovsky stain, Magn. 400×

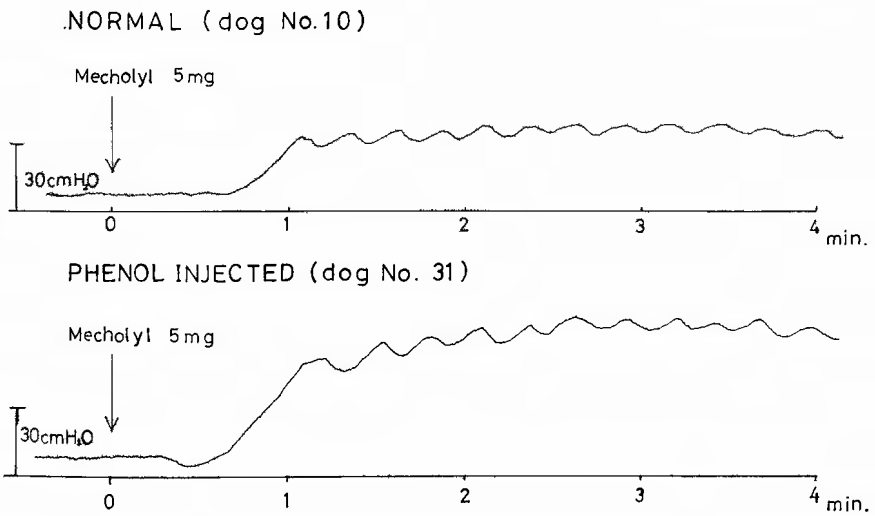

Fig. 4. Changes in LES pressure after intramuscular Mecholyl (5mg) injection Note the marked increase in LES pressure in phenol-injected dogs.

among nerve cells and acted as receptor of stimulation from the extrinsic nerve were observed. Gliocytes appeared here and there around normal nerve cells (Photo 3)[8].

② Phenol-injected dogs

Many nerve cells were round-like and these nuclei and nucleoli disappeared for liquefaction. Nerve fibers were wound significantly and cut off in some places. These changes were thought to be irreversible[59] (Photo 4). In other cases, the findings of retraction of nerve cells, granular degeneration and vacuolation of the plasma were present, while in the region of AUERBACH's plexus some of the ganglion cells completely or partly disappeared and were replaced by proliferating collagenous fibers[40][47].

d) Summary

Resting pressure at GEJ showed a significantly high value in the phenol-injected dogs as compared with the normal dogs. On gross observations of the phenol-injected lower esophagus in 19 sacrificed dogs, the muscular layer was slightly hypertrophic but the mucosa showed no pathological change and significant cicatricial stenosis did not appear in any dog. The LES in the phenol-injected group show hypersensitivity to Mecholyl, and its intraluminal pressure increased dominantly in reponse to Mecholyl injection. This result suggests that AUERBACH's plexus was destroyed completely in these dogs. On histological observations of 19 dogs that survived more than one month after phenol injection, degeneration or destruction of AUERBACH's plexus were seen in 16 of the 19 dogs. It was shown that aganglionic segment of the lower esophagus resulted from the destruction of AUERBACH's plexus when phenol was injected carefully and at a minimum dose (3～4ml). Then three dogs without degeneration or destruction of AUERBACH's plexus and five other dogs which showed values less than 30cm H_2O in resting pressure at GEJ were excepted from the following examinations of gastrointestinal hormones.

2) Change in LES pressure in response to tetragastrin

a) Change in LES pressure in response to intravenous injection of 5μg/kg of tetragastrin

Studies were performed on 10 achalasia-like dogs and nine normal dogs. Mean resting pressure at GEJ was 40.3 ± 2.58 cmH_2O in achalasia-like dogs while it was 20.8 ± 1.87 cmH_2O in normal dogs. Open tip was anchored in the same position as Mecholyl injection. Tetragastrin at a dose of 5μg/kg was injected intravenously into each dog. After tetragastrin injection, LES pressure increased within one minute, attained to peak-responded pressure 3～5 minutes later and returned to initial resting pressure within 15 minutes. After tetragastrin injection, LES pressure in achalasia-like dogs increased from a mean resting pressure of 8.4 ± 0.50 cmH_2O to a mean peak-responded pressure of 65.0 ± 3.67cm H_2O, while LES pressure in normal dogs increased from 7.0 ± 0.82 cmH_2O to 40.1 ± 2.44 cmH_2O. Mean pressure difference was 56.6 ± 3.34 cm H_2O in achalasia-like dogs, while it was 33.6 ± 2.44 cmH_2O in normal dogs (Tab. 2) (Fig. 5, 6). In comparison with increases in LES pressure in response to tetragastrin

Table 2. LES pressure responses to intravenous tetragastrin (5μg/kg) injection

normal dog			achalasia-like dog		
resting pressure	peak pressure	difference	resting pressure	peak pressure	difference
7	48	41	7	44	41
6	38	32	8	67	59
5	45	40	8	75	67
10	51	41	12	81	69
6	30	28	9	54	45
5	39	34	8	64	56
5	44	39	8	72	64
7	33	26	9	75	66
12	33	21	6	48	42
			9	66	57
$\bar{X}$ 7.0	40.1	33.6	8.4	65.0	56.6
1SE 0.82	2.44	2.44	0.50	3.67	3.34

$\bar{X}$=mean unit=cmH_2O

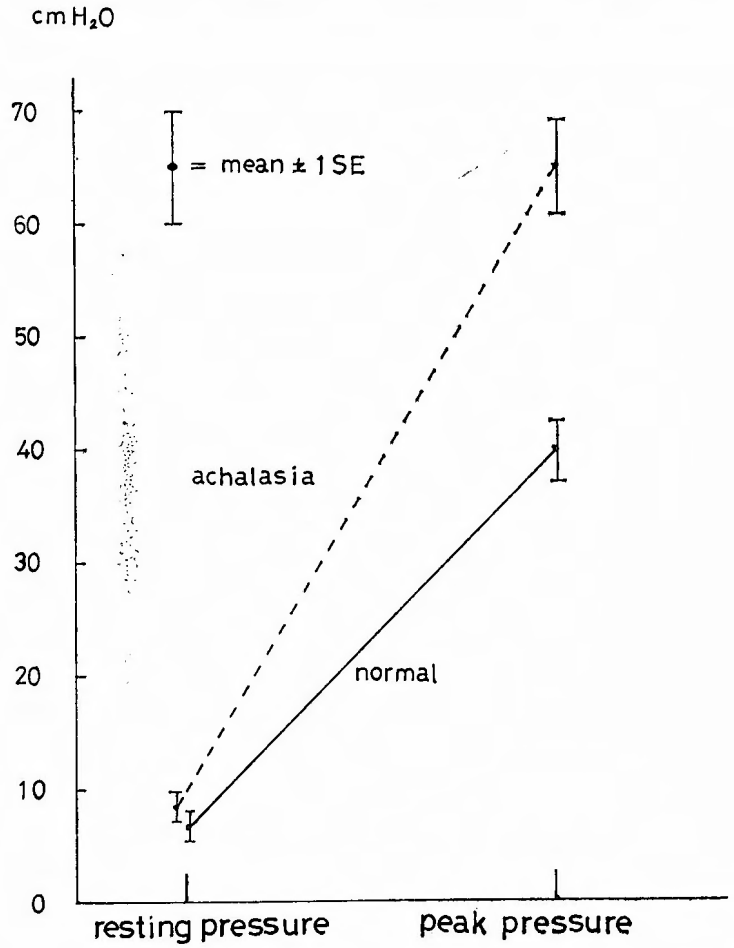

Fig. 5. Comparison of LES pressure responses to intravenous tetragastrin (5μg/kg) injection between normal (9 Cases) and achalasia groups (11 Cases).

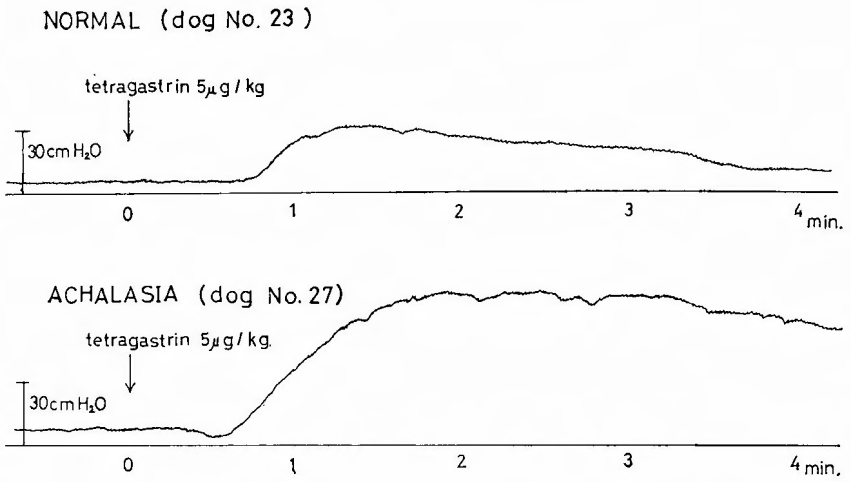

Fig. 6. Changes in LES pressure after intravenous tetragastrin (5μg/kg) injection
Significant increase in LES pressure appeared in achalasic sphincter.

between achalasia-like dogs and normals, a significant difference was observed. The pressure difference was statistically great in achalasia-like dogs ($p<0.01$).

b) Dose-response curves of increase in LES pressure to tetragastrin injection

Studies were performed on normal dog with 23 cmH_2O of resting pressure at GEJ and achalasia-like dog with 52 cmH_2O of resting pressure at GEJ. Tetragastrin at doses of 0.5, 1.0, 2.5, 5.0, 7.5 and 10.0μg/kg, respectively, were injected into each dog. The degree of increase in LES pressure in response to tetragastrin was indicated by pressure differences. In normal dog, pressure differences were 26 cmH_2O with the

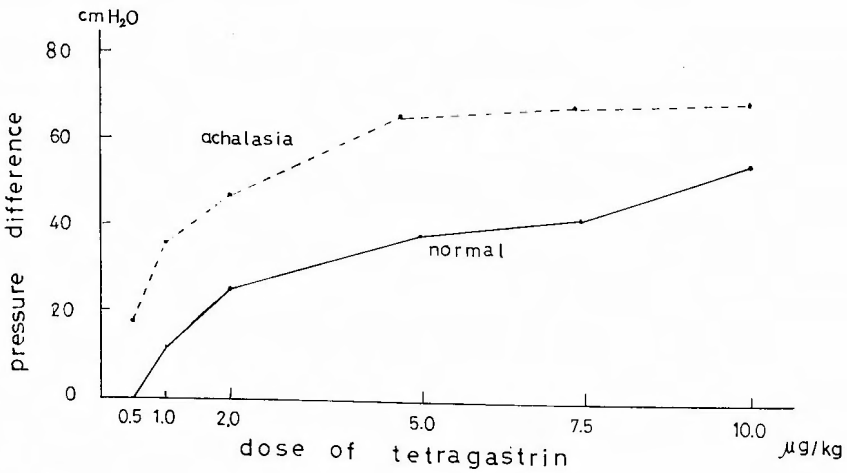

Fig. 7. Dose-response curves of change in LES pressure expressed as a pressure difference between peak responded and initial resting pressures to tetragastrin in μg/kg.

dose of 2.0μg/kg of tetragastrin and 39 cmH_2O with the dose of 5.0μg/kg, while in achalasia-like dog they were 48 cmH_2O and 66 cmH_2O, respectively. Dose-response curves were expressed as pressure difference against dose of tetragastrin in μg/kg. In achalasia-like dog, increase in LES pressure was clearly observed with a small dose of tetragastrin. Dose-response curve in achalasia-like dog shifted to the left in comparison with normal dog. These results proved that LES in achalasia-like dog shows hypersensitivity to tetragastrin (Fig. 7).

3) Changes in LES pressure in response to secretin

The change in LES pressure in response to secretin alone was slight in both normal and achalasia-like dogs. When rapid intravenous injection of secretin was performed, LES pressure increased to a certain degree, such as 3$\sim$5 cmH_2O. Secretin which was used in this study was not pure substance and it contained small doses of gastric inhibitory polypeptide (GIP), cholecystokinin-pancreozymin (CCK-PZ) and other gastrointestinal hormones[43]. On this point it was considered hat slight increase in LES pressure in response to secretin had some relation to the other gastrointestinal hormones. LES pressure showed only a slight change after intravenous injection of secretin at the dose of 5 CHRU/kg/5min.. Therfore, it was judged that intravenous injection of secretin alone had no effect on resting LES pressure.

It was known that gastrin and secretin have antagonistical effects on each other during gastric acid secretion[43]. In this study, the combination effect of gastrin and secretin on LES pressure was examined. Studies were performed on four normal and five achalasia-like dogs. First, tetragastrin at the dose of 5μg/kg was injected intravenously into each dog, and next using the same animals, secretin at the dose of 5 CHRU/kg/5min. was injected intravenously, and after one minute the same dose of tetragastrin was injected. The change in LES pressure was measured and investigated. In the normal group, LES pressure increased from 5.8 ± 0.96 cmH_2O to 38.8 ± 2.46 cm H_2O in response to intravenous tetragastrin injection alone, while it increased from 6.0 ± 0.82 cmH_2O to 25.3 ± 2.75 cmH_2O in response to a previous intravenous secretin injection and the following intravenous tetragastrin injection. Increase in normal LES pressure in response to tetragastrin was inhibited by secretin with statistical significant difference. In the achalasia-group, LES pressure increased from 8.8 ± 0.86 cmH_2O to 72.8 ± 4.46 cmH_2O in response to tetragastrin alone, while it increased from 9.4 ± 1.08 cm H_2O to 53.3 ± 3.61 cmH_2O in response to secretin and tetragastrin. Increase in achalasic LES pressure in response to tetragastrin was inhibited by secretin, the same as normal (Table 3, Fig. 8). However, regarding this inhibitory effect of secretin on increase in LES pressure in response to tetragastrin, its percent reduction was not significantly different between normal and achalasia groups.

4) Change in LES pressure in response to cholecystokinin-pancreozymin (CCK-PZ)

It was necessary to consider that CCK-PZ used in this study was not pure

Table 3. LES pressure responses to tetragastrin (5μg/kg) alone and identical dose of tetragastrin with background intravenous injection of secretin (5CHRU/kg/5min.)

		tetragastrin 5μg/kg alone			secretin 5 CHRU/kg/5min.+tetragastrin 5μg/kg		
		resting pressure	peak pressure	difference	resting pressure	peak pressure	difference
normal group		6	38	32	6	30	24
		6	45	40	6	30	24
		5	39	34	5	21	16
		7	33	26	7	20	13
	$\bar{X}$	5.8	38.8	33.0	6.0	25.3	19.3
	1SE	0.96	2.46	2.88	0.82	2.75	2.81
achalasia group		8	67	59	8	50	42
		12	81	69	12	64	52
		8	64	56	8	42	34
		7	86	69	7	56	49
		9	66	57	12	54	42
	$\bar{X}$	8.8	72.8	62.0	9.4	53.3	43.8
	1SE	0.86	4.46	2.90	1.08	3.81	3.14

$\bar{X}$=mean. unit=cmH_2O

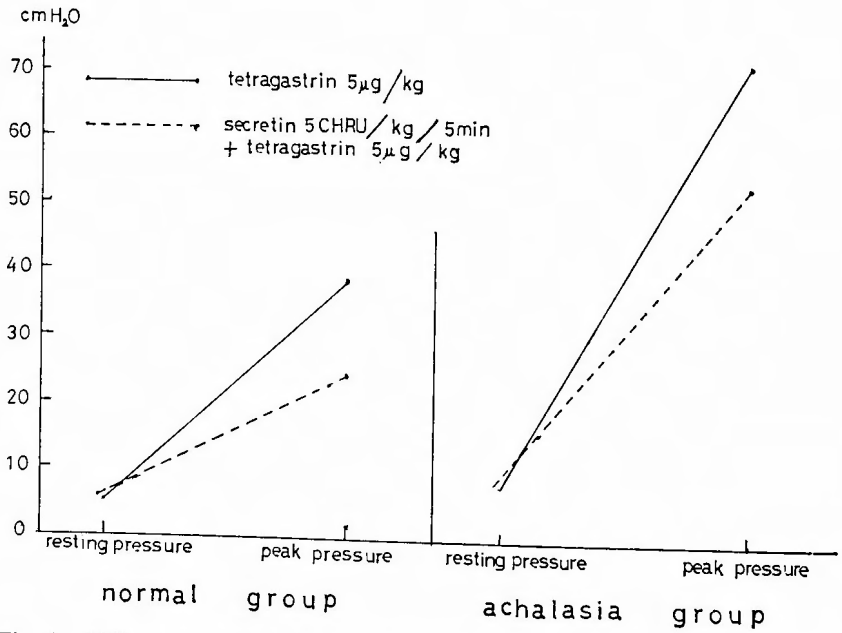

Fig. 8. LES pressure after intravenous tetragastrin (5μg/kg) injection alone and with background intravenous injection of secretin, 10CHRU/kg/5min.

substance and contained small doses of GIP, secretin and other gastrointestinal hormones[43]. Studies were performed on three normal and three achalasia-like dogs. After intravenous injection of CCK-PZ at the dose of 2.5 CHRU/kg, LES pressure increased in both normal and achalasia-like dogs. LES pressure increased from 9.0±1.25 cmH_2O to 30.0± 3.06 cmH_2O in the normal group, while it increased from 14.0±1.15cm H_2O to 60.0± 4.16 cmH_2O in the achalasia group (Table 4). The comparison of increase in LES pressure

Table 4. LES pressure responses to intravenous CCK-PZ (2.5CHRU/kg) injection

	normal group			achalasia group		
	resting pressure	peak pressure	difference	resting pressure	peak pressure	difference
	8	24	16	14	52	38
	7	34	27	12	66	54
	12	32	20	16	62	46
$\bar{X}$	9.0	30.0	21.0	14.0	60.0	46.0
1SE	1.52	3.06	3.32	1.15	4.16	4.62

$\bar{X}$=mean unit=cmH_2O

in response to CCK-PZ between normal and achalasia groups was significantly different. Next, CCK-PZ at doses of 0.5, 1.0, 2.5 and 5.0 CHRU/kg, respectively, were injected into normal and achalasia-like dogs. In achalasia-like dogs, the increase in LES pressure was remarkable with a small dose of CCK-PZ. Dose-response curves showed a similar tendency to those when tetragastrin was injected. After intravenous injection of CCK-PZ at

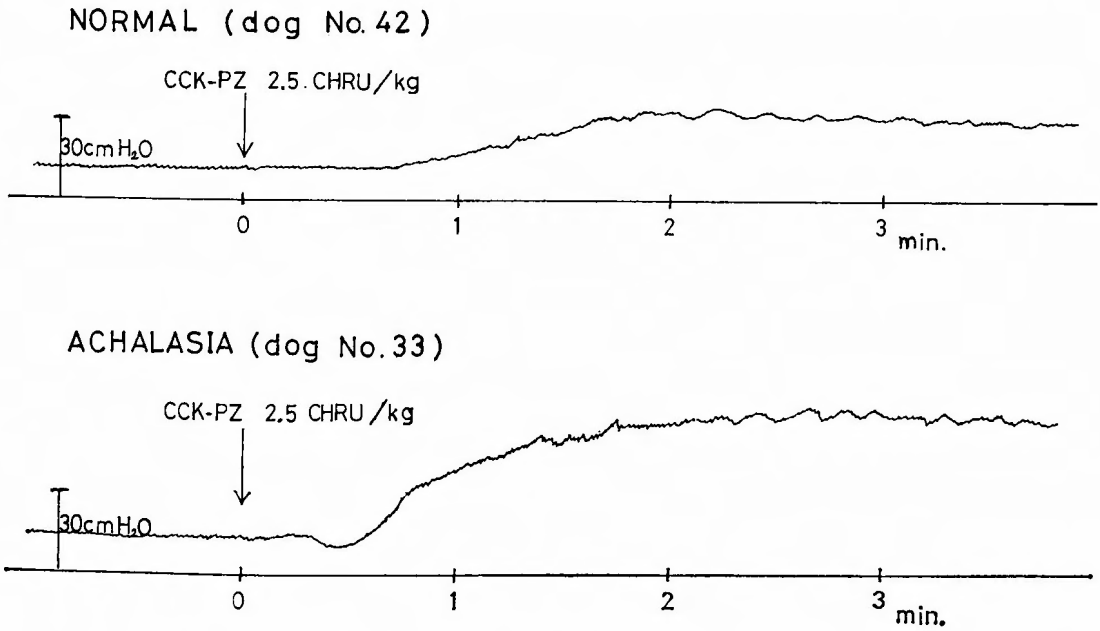

Fig. 9. Changes in LES pressure after intravenous CCK-PZ (2.5CHRU/kg) injection in normal and achalasic dogs.

the dose of 2.5 CHRU/kg, LES pressure increased from 12 cmH_2O to 32 cmH_2O in normal dog, while it increased from 16 cmH_2O to 62 cmH_2O in achalasia-like dogs (Fig. 9). It was evident that achalasic LES show hypersensitivity to CCK-PZ in the same manner as tetragastrin.

5) Change in serum gastrin level following intramuscular Mecholyl injection

Studies were performed on five normal dogs. In this study, mean serum gastrin concentration in normal dogs under fasting and satisfactory anesthesia was 71.3±4.12 pg/ml. Aftter an intramuscular injection of Mecholyl at the dose of 10 mg, serum gastrin concentration indicated high levels, especially 2～10 minutes after Mecholyl injection (Fig. 10). However, serum gastrin concentration after Mecholyl injection

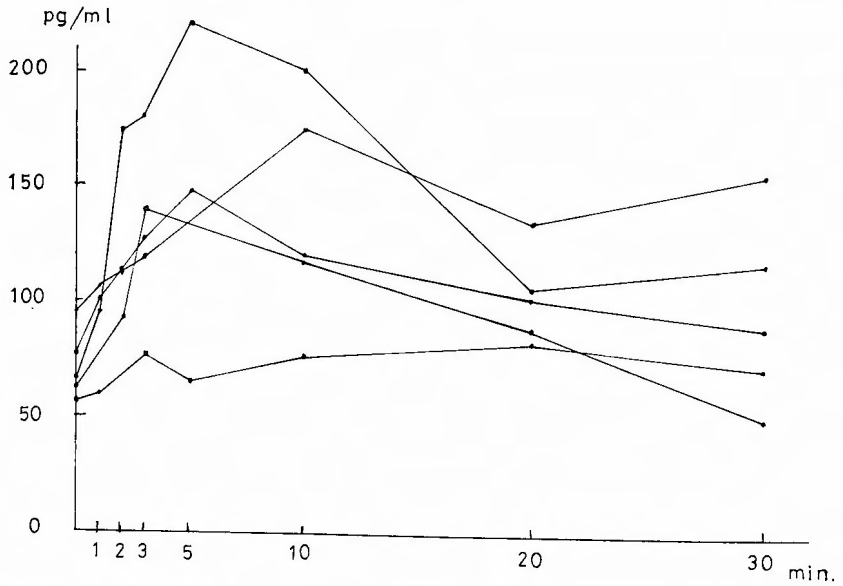

Fig. 10. Changes in serum gastrin levels following intramuscular Mecholyl (10mg) injection.

indicated considerable dispersion in each case. In an extraordinary case, serum gastrin concentration indicated 62 pg/ml in resting state and then, 5 minutes after Mecholyl injection it indicated 220 pg/ml.

Ⅵ. Examination of clinical cases

Recently, seven patients with ahcalasia of the esophagus were operated upon in our surgical clinic. These cases are shown according to "Descriptive Rules for Achalasia of the Esophagus"[36] (Table 5). On all patients, fluoroscopic observations were performed following intramuscular injection of 10mg of Mecholyl. Tonic contractions began in the lower esophagus and gestroesophageal junction and then narrow segment extended upward. Six patients complained of severe pain in the retrosternal and epigastric regions. Examination of electroencephalogram (EEG) were performed on six patients. Diagnoses of EEG were within normal limits in three patients, spike and wave of 1

Table 5. Clinical Cases (patients with achalasia)

	Case	duration of symptom prior to operation	maximum width of esophagus (grade of dilatation)	type of dilatation
1.	15♀	1Y. 2M.	5.0cm (II)	F
2.	76♂	10Y.	3.6cm (II)	SP
3.	15♂	1Y. 8M.	4.4cm (II)	SP
4.	29♀	20Y.	6.0cm (III)	S
5.	38♀	1Y. 2M.	6.5cm (III)	S
6.	63♂	2Y.	5.0cm (II)	F
7.	52♂	20Y.	6.7cm (III)	S

F=frask type SP=spindle type S=sigmoid type

type in one patient (Case 1) and abnormal slow wave and θ burst in two patients (Cases 4 and 5). HOLLANDER test was performed on four patients. According to HOUANDER'S criteria, a negative response was shown in two patients (Cases 4 and 7). Therefore, it was suspected that a high degree of damage to the vagal trunks were present in these two patients. Intraluminal pressure measurements were performed on four patients. In all patients the lack of peristalsis on the lower esophagus after swallowing was obseved. In one patient (Case 4), polyethylene tube did not enter into the stomach. In three other patients, each resting pressure at GEJ was indicated at 38 cm H_2O in Case 5, at 38 cmH_2O in Case 6 and at 45 cmH_2O in Case 7. Measurements of LES pressure after intramuscular injection of 5 μg/kg of tetragastrin were performed on two patients. In one patient (Case 5), open tip was anchored in the position, 3cm oral to RIP, the LES pressure increased from a resting pressure of -2 cmH_2O to a peak-responded pressure of 30 cmH_2O after tetragastrin injection. In another patient (Case 7), the LES pressure increased from 12 cmH_2O to 45 cmH_2O. In both cases the LES pressures increased and then returned to initial resting pressures within 7$\sim$10 minutes after tetragastrin injection. Fluoroscopic observaitons following intramuscular injection of 5μg/kg of tetragastrin showed the contractions of the lower esophagus and considerable increase in peristaltic activity. The contrast material did not enter into the stomach (Photo 6). Only one patient complained of such severe pain usually complained after Mecholyl injection. From these results it was proved that not only Mecholyl but also exogeneous gastrin abnormally elevate the LES pressure in patients with achalasia. Therefore, reaction of the LES in response to exogenous gastrin was useful for preoperative diagnosis of esophageal disorders.

JEKLER & LHOTKA's method[37] was performed on these seven patients. In one patient (Case 5), dilatation of the esophagus reduced 1.5 months after operation and the contrast material smoothly entered into the stomach. In this case, preoperative resting pressure at GEJ indicated 38 cmH_2O, but it decreased to 17 cmH_2O postoperatively. This postoperative resting pressure at GEJ was appropriate value to prevent

Photo 5

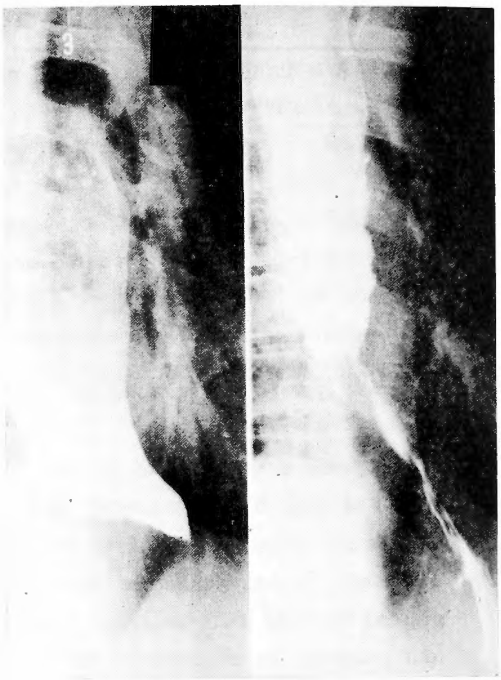

Photo 6

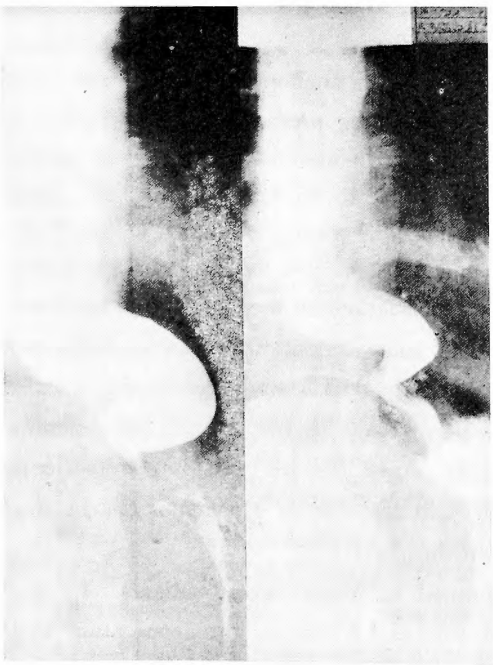

Photo 7

Photo 5. Roentgen appearance during Mecholyl test in Case 6.
Resting state is shown on the left side. The appearance 5min. after intramuscular Mecholyl injection is shown on the right side.

Photo 6. Roentgen appearance after intramuscular tetragastrin(5μg/kg) injection in Case 6.
Resting state is shown on the left side. The appearance 5min. after tetragastrin injection is shown on the right side.

Photo 7. Roentgen appearance in Case 5.
Preoperative state is shown on the left side. The appearance 1.5 months after Jekler-Lhotka's operation is shown on the right side.

postoperative reflux esophagitis[4)54)]. Six patients except one patient (Case 4) made favorable progress after the operation and did not complain of symptoms of reflux esophagitis and swallowing disturbance. One patient (Case 4) who had suffered from symptoms for 20 years prior to operation and whose esophagus showed sigmoid type fluoroscopically, complained of difficulty in swallowing after the operation. In this patient, esophagocardiectomy with small bowel interposition between distal esophagus and stomach was carried out 1.3 years after the previous operation and her postoperative course was satisfactory.

Discussion

Although there have been many attempts to produce achalasia of the esophagus in experimental animals, no one but experimental achalasia induced by destruction of AUERBACH's plexus[1)] showed that hypersensitivity to Mecholyl[27)39)] which was used to differentiate achalasia from other types of esophageal disorders in clinical cases. In the experimental achalasia induced by bilateral cervical vagotomy[11)], destruction of the center of the vagus nerve[26)], prolonged cholinesterase inhibition[24)] and so forth, aperistalsis and lack of relaxation after swallowing in the lower esophagus appeared, but specific reaction to Mecholyl was not present[11)]. ROTH[52)] denied "transsynaptic degeneration", that is, the view that secondary degeneration of AUERBACH's plexus was produced following destruction of the center of the vagus nerve or bilateral vagotomy. GREENWOOD, et al.[23)] confirmed that the function of the gastroesophageal junction was still preserved after all extrinsic nerve supply were excluded and suggested that the gastroesophageal junction contained an instrinsic factor in itself and had an automatism. SWENSON[56)] confirmed that peristaltic activity of the lower esophagus recovered within a week after bilateral cervical vagotomy in cat and suggested that the short reflex arc which contained AUERBACH's plexus was present. On the other hand, BINDER[7)] reported that degeneration of AUERBACH's plexus was revealed after cervical vagotomy in monkey. CASSELLA[10)] reported that the change of AUERBACH's plexus was secondary to central change. OKAMOTO[46)] proposed that achalasia which was caused by myenteric nerve disorders should be discriminated from other types of esophageal disorders and named "dysganglionic achalasia". The author injected 5% phenol into the muscular layers of the lower esophagus in dogs for the purpose of destroying AUERBACH's plexus, then the resting pressures at GEJ in phenol-injected dogs revealed significantly high values. High pressure values at GEJ in phenol-injected dogs might be caused by cicatricial stenosis and adhesion to some extent. However, COHEN[15)], using a constantly infused recording system, has shown that LES pressure in patients with achalasia is twice that of normal subjects. The author also demonstrated the hypertonicity of the gastroesophageal junction in achalasia-like dogs. The hypersensitivity of LES in patients with achalasia to Mecholyl was explained as follows : Disappearence or degeneration of myenteric nerve plexus, especially postganglionic parasympathetic plexus alterations, were observed

in these patients. Therefore, according to CANNON's law of autonomic denervation[9)30)31)], the hypersensitivity to parasympathicomimetic agents appeared. In this study, the LES in phenol-injected dogs showed hypersensitivity to Mecholyl. All 19 dogs had survived for more than one month after phenol injection and were finally sacrificed for autopsy. On histological examinations with hematoxylin-eosin and modified BIRSHOVSKY's stains, degeneration or destruction of AUERBACH's plexus were confirmed in 16 of the 19 dogs. In phenol-injected dogs, resting pressure at GEJ increased, the LES showed hypersensitivity to Mecholyl and destruction or degeneration of AUERBACH's plexus appeared. Therefore, using phenol-injected dogs as achalasia dogs, examinations of gastrointestinal hormones were performed.

Gastrin is polypetides which consists of 17-amino acids sequence. In this study, tetragastrin which was C-terminal tetrapeptide, was used as exogenous gastrin. Tetragastrin at the dose of 5μg/kg was injected intravenously into nine normal and 10 achalasia dogs. Then, the LES pressure increased significantly in the achalasia group. Additionally, tetragastrin at each dose of 0.5, 1.0, 2.0, 5.0, 7.5 and 10.0μg/kg, respectively, was injected into normal and achalasia dogs. Then, in achalasia dog, LES pressure increased significantly with a small dose of tetragastrin and dose-response curve shifted to the left in comparison with that in normal dog. These results proved that LES in achalasia dog showed hypersensitivity to tetragastrin as well as Mecholyl.

Since CASTELL, et al[12)]. reported that LES pressure in a normal person increased after subcutaneous injection of Histalog at the dose of 2mg/kg or gastric alkalization with 0.1N NaOH causing apparent release of endogenous gastrin, and also after subcutaneous injection of exogenous gastrin, that is, gastin like-pentapeptide, many reports[6)16)] on the correlation between gastrin and LES had been presented. On the other hand, COHEN[16)] reported that the LES in patients with achalasia was supersensitive to exogenous gastrin I. CANNON's[9)] law of autonomic denervation has shown that denervation leads to supersensitivity not only to natural neural transmitters but also nonspecifically to other cheminal stimulants, and VIZI[60)], et al. confirmed that gastrin and cholecystokinin-related polypeptide released acetylcholine from the AUERBACH's plexus of the longitudinal muscle strip of guinea pig ileum. Therefore, it was confirmed that LES in patients with achalasia shows hypersensitivity to gastrin as well as Mecholyl. COHEN, et al[16)]. confirmed that LES pressure in patients with achalasia was twice that of normal subjects and emphasized that tonus of LES was maintained by endogenous gastrin. In this study, the resting pressure at GEJ in achalasia dogs revealed significantly high values. LIPSHUTZ[42)] reported that hypogastrinemia was revealed in the patients with lower esophageal sphincter incompetence. On the other hand WRIGHT[33)62)63)] reported that there was no correlation between LES pres ure and serum gastrin levels : for example, a patient with pernicious anemia who showed abnormally high levels of serum gastrin but whose LES pressure indicated 20 cmH_2O that was within normal range. Many investigators[21)] reported that serum gastrin levels in patients

with achalasia were within normal range : therefore, it was neglected that hypergastrinemia was the direct cause of achalasia.

Secretin is polypeptide which consists of 27 amino acids sequence, and its primary actions is stimulation of the pancreatic secretion and one of its additional actions seems to be related to the function of LES. It was evident that gastrin and secretin have antagonistical effects on each other during gastric acid secretion. COHEN and LIPSHUTZ[15] reported that human LES pressure increased in response to intravenous injection of synthetic gastrin I but its increase was inhibited significantly by exogeneous secretin injection or by duodenal acidification causing release of endogeneous secretin. On the other hand, when previous gastric alkalization with 0.1N NaOH causing release of endogeneous gastrin was performed, and then, exogeneous secretin was injected intravenously continuously, human LES pressure decreased significantly about three minutes after secretin injection. In this study, increases in LES pressure in both normal and achalasia dogs in response to tetragastrin were inhibited by background injection of secretin but there was no significant difference in the per cent reduction between normal and achalasia groups. Therefore it was considered that this inhibitory effect of secretin was not related to destruction or degeneration of AUERBACH's plexus, but secretin acted antagonistically to the effect of gastrin.

It was proved by JORPES and MULT[43] that cholecystokinin and pancreozymin were the same substance. Its primary action was contraction of the gall bladder and secretion of pancreatic enzyme. Cholecystokinin-pancreozymin (CCK-PZ) is polypeptide which consists of 33 amino acids sequence, and its C-terminal six amino acids sequence is just the same as that of gastrin[17]. In this study, after intravenous injection of CCK-PZ at the dose of 2.5 CHRU/kg, LES pressure increased in both normal and achalasia groups. Increase in LES pressure in achalasia group was significantly high as compared with that in normal group. Therefore, it was evident that achalasic LES showed hypersenstivity to CCK-PZ in the same manner as tetragastrin. It was said that CCK-PZ alone stimulated LES but CCK-PZ competitively inhibited the effect of gastrin on LES contraction while gastrin competitively inhibited the effect of CCK-PZ on pyloric muscle contraction. RESIN[50] reported that the calculated maximal decrease which could be produced by intravenous injection of octapeptide of cholecystokinin was 60% of the resting LES pressure. GROSSMAN postulated that the similarity of C-terminal amino acids of gastrin to that of cholecystokinin makes it probable that both hormones have an affinity for the same receptor site. Therefore, the effect of gastrin on LES might be inhibited by the competitive effect of CCK-PZ. In this study, competitive inhibitory effect of CCK-PZ to endogeneous gastrin was not evident.

JENNEWEIN[28][35][38] reported that glucagon causes a decrease in resting sphincter pressure in both man and dog and antagonizes the pentagastrin-induced pressure increase of the LES.

ROLING[51] reported that Urecholine produced increases in LES pressure in both

normal subjects and patients with sphincter incompetence, and this response appeared to be mediated at least partially through release of endogeneous gastrin. In this study, after intramuscular injection of Mecholyl, that is, cholinergic agent, at the dose of 10 mg, serum gastrin concentrations in dogs indicated high levels. Therefore, increase in LES pressure in response to Mecholyl might appear to be mediated partially through release of endogeneous gastrin but the author regarded this response mostly as a direct effect of Mecholyl.

As surgical treatment for achalasia of the esophagus, HELLER-ZAAIJER's extramucosal esophagocardiomyotomy and its modified procedures[5], that is, GIRARD's method[14], PETROVSKY's method[48], DIRVANA-ÇILINGIROGLU's method[19] and JEKLER-LHOTKA's method[37], and then MARWEDEL-WENDEL's cardioplasty[13], THAL's fundic patch method[25][58], HEYROVSKY's subphrenic side-to-side esophagogastrostomy[57] and its modified procedure, that is, GRÖNDAHL's method and esophagocardiectomy[57] had been performed. JEKLER-LHOTKA's method has been selected for use in our surgical clinic for reasons that its operative technics were comparatively easy, significant improvement of passage disturbance was obtained and moreover, reflux esophagitis and other postoperative complications were rare[32]. In a patient (Case 5), preoperative resting pressure at GEJ indicated 38 cm H_2O. However, 45 days after JEKLER-LHOTKA's operation it decreased to 17 cmH_2O, then the suitable high pressure zone remained postoperatively to prevent reflux esophagitis.

Conclusion

Using adult mongrel dogs, experimental achalasia dogs were produced according to DELOYER's method with an injection of 5% phenol solution into the muscular layers of the lower esophagus. The effects of gastrointestinal hormones, such as gastrin, secretin and CCK-PZ, on the LES in normal and achalasia dogs were investigated, and clinical cases of achalasia were also examined.

1) Although 30 dogs were injected with 5% phenol solution, only 19 dogs survived more than one month after phenol injection. In these 19 dogs only 13 dogs were regarded as most satisfactory experimental achalasia dogs from the results of measurements of LES pressure in response to Mecholyl and histological examinations.
2) Increase in LES pressure in response to tetragastrin was satistically great in the achalasia group as compared with that in normal group. Moreover, dose response curve of the LES to each dose of tetragastrin in μg/kg in achalasia dog shifted to the left as compared with that in normal dog. Therefore it was proved that the LES in achalasia dogs showed hypersensitivity to tetragastrin.
3) Intravenous injection of secretin alone had no significant effect on resting LES pressure in both normal and achalasia groups. Increase in LES pressure in response to tetragastrin was inhibited by background injection of secretin in both normal and achalasia groups. However, as concerns this inhibitory effect of secretin on the increase in LES pressure in response to tetragastrin, its per cent reduction was not significantly different

between normal and achalasia groups. Therefore, it was considered that this effect of secretin was not related to destruction or degeneration of AUERBACH's plexus but secretin acted antagonistically to the effect of gastrin.

4) LES pressure increased in response to an intravenous injection of CCK-PZ. Moreover, achalasic LES showed hypersensitivity to exogeneous CCK-PZ in the same manner as gastrin. Competitive effect between gastrin and CCK-PZ was not evident in this study.
5) Following an intramuscular injection of Mecholyl at the dose of 10mg, serum gastrin level indicated high values in normal dogs. Therefore, increase in LES pressure in response to Mecholyl might seem to be mediated partially through release of endogeneous gastrin but the author regarded this increase in LES pressure mostly as a direct effect of Mecholyl.
6) In patients with achalasia, the LES showed strong contraction and significant increase in pressure by fluoroscopy and measurements of intraluminal pressure in response to intramuscular injection of tetragastrin at the dose of 5μg/kg. Therefore, this positive response of the LES to tetragastrin was useful for preoperative diagnosis of patients with achalasia.
7) JEKLER-LHOTKA's method proved to be an excellent surgical procedure for achalasia of the esophagus because passage disturbance was improved and then suitable high pressure zone to prevent postoperative reflux esophagitis was reconstructed at the gastroesophageal junction.

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和文抄録

食道アカラシアの病態生理におけるガストリンを初めとする消化管ホルモンの役割

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食道アカラシアの病態生理におけるガストリンを初めとする消化管ホルモンの役割を究明する目的で,雑種成犬の下部食道筋層内に5%フェノールを注入し,1カ月後の食道内圧検査,メコリール試験,鍍銀染色標本などで食道アカラシア性変化をきたしたことが確認されたアカラシア犬とコントロールの正常犬において,ガストリン,セクレチン,コレチストキニンなどの消化管ホルモンの作用を食道内圧測定によって明らかにした.また食道アカラシア臨床例においても,テトラガストリン5μg/kg筋注時の下部食道内圧測定,レ線検査を行い,以下のことを明らかにした.

1) テトラガストリン5μg/kgの静注によってアカラシア犬は正常犬に比較して著明な下部食道内圧の上昇をきたし,さらに各種濃度のテトラガストリン投与に対する dose-response curve においてもアカラシア犬のそれは正常犬に比較して左側に偏位していたことから,アカラシア犬の下部食道括約筋は外因性ガストリンに対して過敏性を示すことが明らかとなった.

2) セクレチンの単独静注ではアカラシア犬,正常犬ともにその下部食道内圧は有意の変化を示さなかった.テトラガストリン5μg/kgの静注による下部食道内圧の上昇はセクレチン 5CHRU/kg/5min の静注で抑制された.このセクレチンによる抑制効果は,アカラシア犬,正常犬の間でその減少率に有意の差を認めなかったことから,セクレチンは食道壁内神経叢の病変には関係なく,ガストリンの下部食道内圧上昇作用にのみ拮抗して抑制的に作用すると考えられた.

3) コレチストキニン 2.5CHRU/kg の静注によってアカラシア犬は正常犬と比較して著明な下部食道内圧の上昇をきたした点から,アカラシア犬の下部食道括約筋はガストリンと同様,コレチストキニンに対しても過敏性を示すことを明らかにした.

4) 正常犬におけるメコリール10mg筋注時の血清ガストリン濃度の測定では,筋注後2～10分後に高値を示した.それ故,メコリールによる下部食道内圧の上昇は,その一部分は内因性ガストリンの放出によっておこると推定された.

5) 食道アカラシア臨床例の下部食道はテトラガストリン5μg/kgの筋注によって著明な内圧の上昇をきたし,レ線検査においても下部食道から噴門にかけて強直性収縮がみられたことから,外因性ガストリンに対する下部食道の反応を食道内圧測定,およびレ線検査で観察することは食道アカラシアの術前の特異診断として役立つことが明らかとなった.

6) 食道アカラシアの手術術式として Jekler-Lhotka 法は術式が簡単であり,通過障害を改善するとともに,食道胃接合部に逆流性食道炎を防止する適度の高圧帯を形成しうるのですぐれた手術術式と考えられた.