
原 著

Humoral Factors which Control the Motor-Function of Pedunculated and Free Transplanted Gastrointestinal Tubes for Esophageal Reconstruction

by

SEIJI YUKIMORI

The 2nd Surgical Division, Kyoto University Medical School

(Director : Prof. Dr. CHUJI KIMURA)

Received for Publication Sept. 26, 1969

INTRODUCTION

For esophageal reconstruction after esophagectomy, pedunculated and free transplanted gastrointestinal tubes have been utilized. Especially, the modus of operation utilizing pedunculated gastric or colonic tube is useful. Due to recently advanced small vessel anastomosis technique, many esophageal reconstructive operations by means of free transplanted intestinal tube have been performed and many successful cases have been reported in succession. Therefore, the clinical value of this operation should be regarded as established. However, the fundamental study on this subject has not been sufficiently carried out, especially, the humoral mechanism which is considered to control the motor-function of free transplanted gastrointestinal tubes has not been clarified yet, although a report³⁷⁾ that suggested its possible existence was presented.

Since EDKINS¹¹⁾ presented gastrin hypothesis in 1905, its existence had been even doubtful for many years although it had been studied by several investigators. KOMAROV²²⁾ confirmed that gastrin existed as protein or polypeptide in 1938. In the 1960's pure gastrin has been extracted, its chemical structure has been determined and its synthesis has become possible. Since then, it has been clarified that gastrin is a physiological gastric secretagogue, has direct actions on not only gastric acid and pepsin secretion but also on pancreatic secretion, and possesses various actions in the alimentary tract^{2) 14) 31) 38) 39)}.

Using gastrin-like tetrapeptide, the author has performed various experimental studies to examine the effect of gastrin on the gastric and intestinal motility and has been able to obtain interesting information. Furthermore, esophageal reconstructive cases utilizing pedunculated colonic tube in our surgical clinic, in which the gastrin mechanism may be concerned, will be scrutinized.

I. EFFECT OF GASTRIN-LIKE TETRAPEPTIDE ON THE MOTOR-FUNCTION OF VARIOUS PORTIONS OF THE GUT

1) *Materials and Methods*

Adult mongrel dogs of both sexes ranging in weight from 8 to 14 kg were used.

a) Jejunum and Ileum : For measurement of the movement in these portions, Thirty

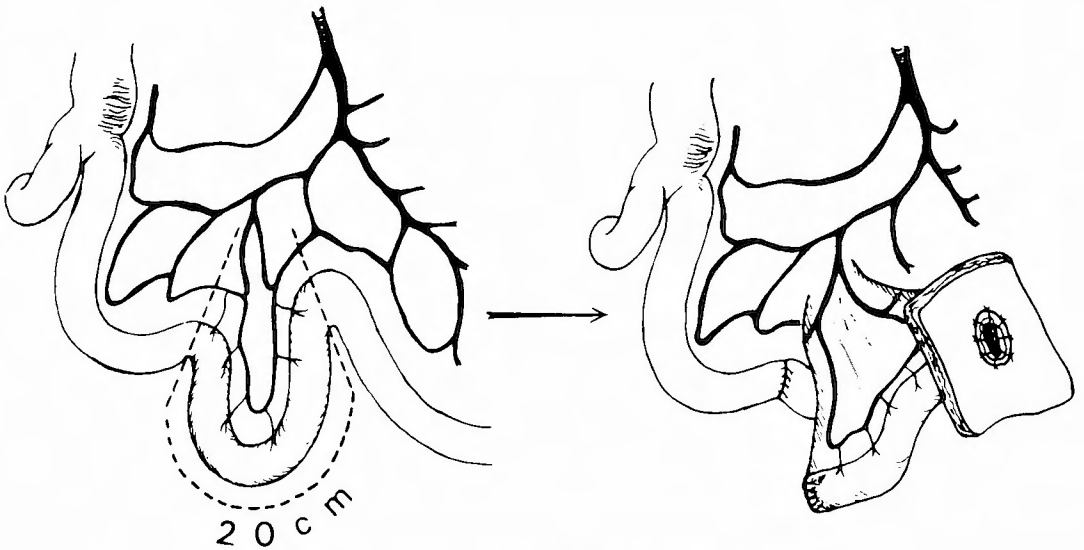


Fig. 1 Diagram of the method used to construct the Thiry fistula.

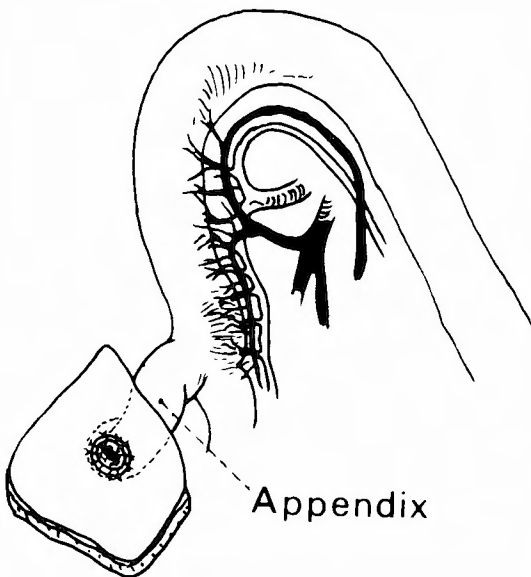


Fig. 2 Diagram of the method used to construct an appendical fistula.

fistula was made (Fig. 1). Measurement was performed 3 weeks or more after operation by inserting a balloon approximately 10 cm from a stoma of the fistula.

b) The right colon : For measurement of the movement in this portion, appendical fistula was made (Fig. 2). Measurement was performed 3 weeks or more after operation by inserting a balloon approximately 10 cm from a stoma of the fistula.

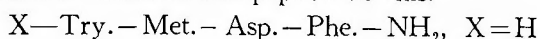
c) The left colon : For measurement, a balloon was inserted approximately 10 cm from the anus.

d) Intraluminal pressure study : The intraluminal pressure in the gut was measured by a miniature balloon which was made of rubber condom, 3 cm in length. Experimental animals, after fasting for over

24 hours, were anaesthetized with intravenous administration of sodium pentobarbital 25 mg per kg and additional administration of 50 mg of this drug when necessary. The rubber balloons were inserted into each portion of the gut as mentioned above.

The balloon was connected through a polyethylene tube, 3 mm in diameter, to the electric manometer of MP-4T type, amplifier of MP-3A type and polygraph of RM-150 type containing amplifier of RB-2 type and recorder of WI-260 TR type (NIHONKODEN. Co. Ltd.).

e) The chemical structure of gastrin-like tetrapeptide used in this study is shown as follows, and it has been already clarified that all physiological functions of natural gastrin are possessed by the same C-terminal tetrapeptide as this.



2) Results

a) Wave patterns : Wave patterns were analysed according to CODE's classification⁹⁾. Wave patterns in the jejunum and ileum provoked by gastrin-like tetrapeptide were regarded as peristalsis with a change of intestinal tonus, which was classified into Type III wave in the small intestine. There was no difference in wave pattern between the jejunum and the ileum. No marked change of wave pattern was found with different doses of the

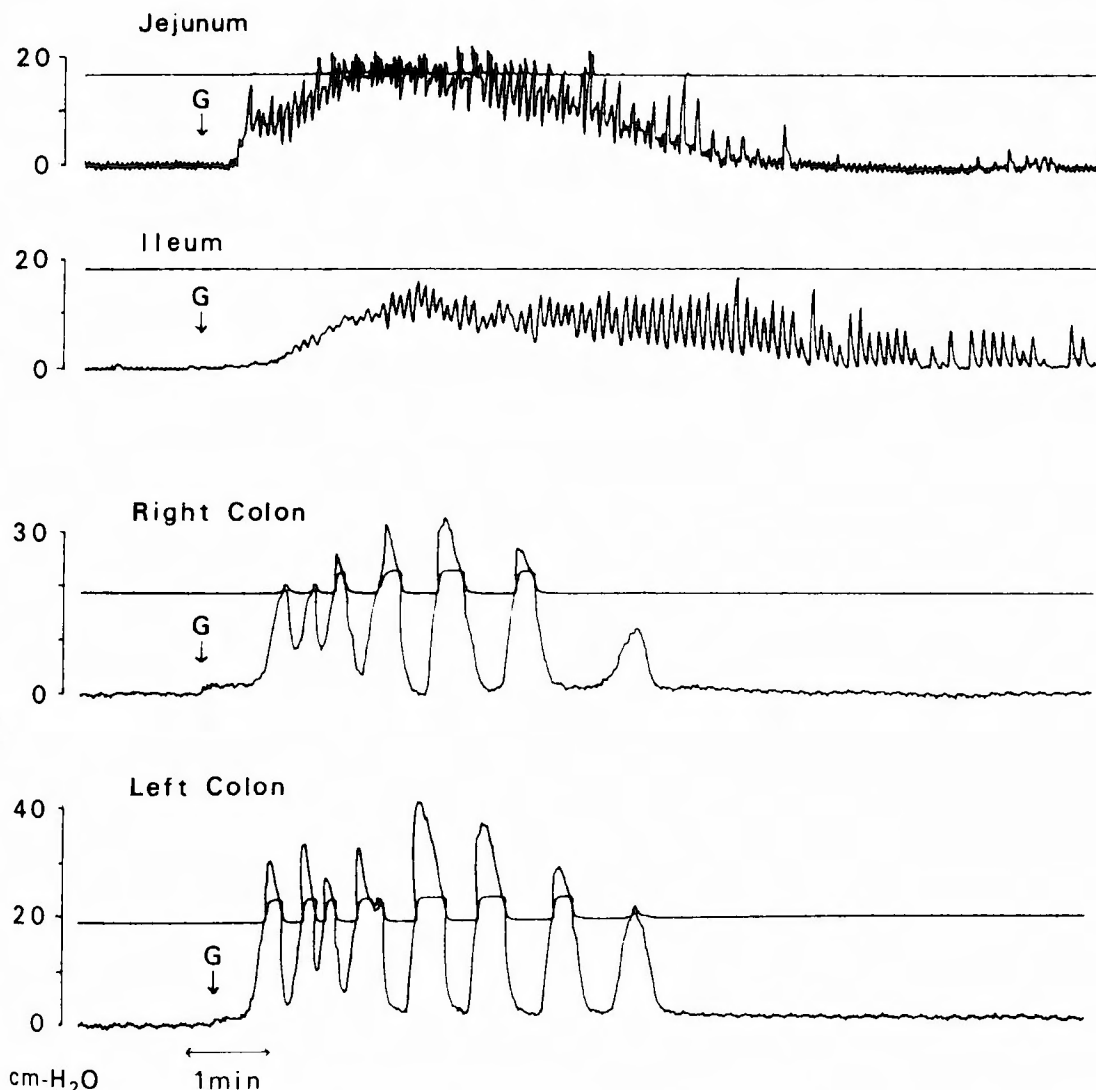


Fig. 3 The effects of a rapid intravenous injection of gastrin-like tetrapeptide, 0.5 μg per kg in dose, on the motor-function of the jejunum, ileum, right colon and left colon of dogs. G : An intravenous injection of gastrin-like tetrapeptide.

tetrapeptide. Wave pattern in the colon provoked by the tetrapeptide had a slightly shorter periodic time than that of Type IV wave in the large intestine, but the pattern of each contraction was a solitary and powerful wave. Therefore, they were classified into the category of Type IV. There was no difference in the pattern between the right half and the left half of the colon (Fig. 3).

b) Dose- Response Curve : For the purpose of a quantitative expression of the intestinal motility, the author has introduced "Motility Index" with which motor-effects were analysed quantitatively. Area "S" obtained by integrating the intraluminal pressure curve, is equal to the work of intestinal peristalsis and proportional to the momentum during "T" minutes.

$$\text{Force (F)} = s \cdot h \cdot A \cdot g$$

s : specific gravity.

h : height of water column.

A : sectional area of water column.

g : gravitation.

$$\text{Momentum (M)} = F \cdot t$$

t : time

$$= s \cdot h \cdot A \cdot g \cdot t$$

Momentum during T minutes

$$= s \cdot A \cdot g \int_{t=0}^{t=T} h \cdot dt$$

$$= K \int_{t=0}^{t=T} h \cdot dt$$

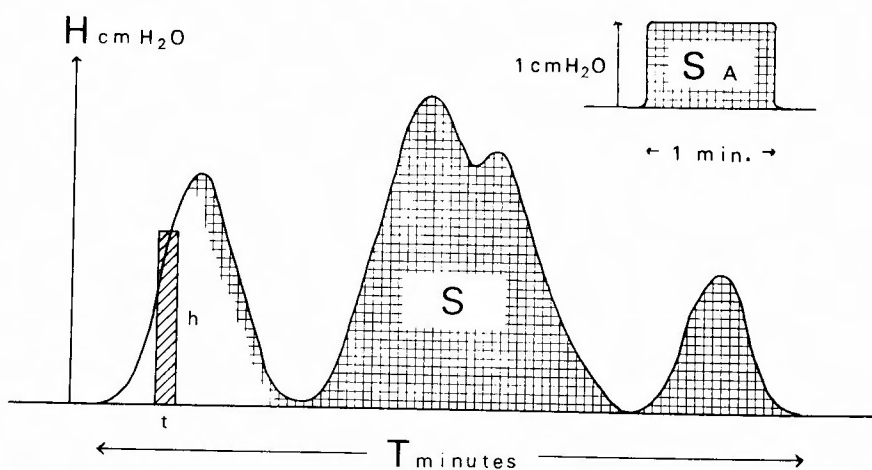


Fig. 4 Motility index is ratio of S to SA. For actual measurement the numbers of 1 mm² section in the areas S and SA are calculated.

"Motility Index" is ratio of "S" to "SA", which is an area occupied when one centimeter water pressure movement has continued for one minute- a unit of momentum. For actual measurement, the numbers of 1 mm² section in the areas S and SA were calculated.

Gastrin-like tetrapeptide was administered from 0.05 to 2.0 μ g per kg in geometrical series and injected rapidly into the lingual vein.

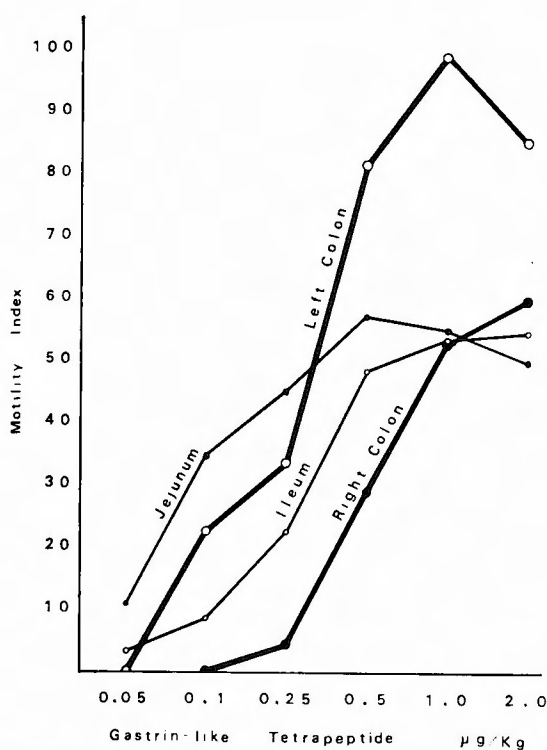


Fig. 5 Dose-response curves for the motility of the jejunum, ileum, right colon and left colon in response to gastrin-like tetrapeptide.

in comparison with the other three portions.

II. EFFECT OF TEST MEAL ON THE MOTOR-FUNCTION OF THE JEJUNUM AND COLON

a) Test meal : Test meal was made as follows. A soup stock was boiled down, by adding 100 ml of water to 100 g of chicken bone. Fifty grams of minced meat and 100 ml of milk were added to the soup stock. Approximately 200 ml of the whole quantity was instilled into the antrum of the stomach through a nutrition catheter. Animals were put in a right lateral position under intravenous anaesthesia of sodium pentobarbital.

b) The movements of the jejunum and colon, provoked by means of the procedure described above, were measured according to the method mentioned before. Using three dogs, six experiments were done respectively on the jejunum and the colon, and in every case, a marked increase in bowel movements was observed. The effects were observed after about fifteen minutes in the jejunum, and in the left colon from 3 to 25 minutes later. Wave patterns of the movements provoked by test meal agreed with those by the tetrapeptide (Fig. 6).

III. INFLUENCE OF DENERVATION ON THE MOTOR EFFECT IN THE COLON PROVOKED BY GASTRIN-LIKE TETRAPEPTIDE

Dogs, whose inferior mesenteric artery had been only ligated and severed previously,

Dose-Response Curves of the jejunum, ileum, right and left colons are shown in Fig. 5. Judging from those of the jejunum, ileum and the right colon, with a lesser dose than 1.0 µg per kg of the tetrapeptide, the dose-response curve of the jejunum was in the extreme left position, that of the right colon, in the extreme right, and that of the ileum transferred in between the two. Namely, to intravenous injection of small doses, the jejunum was the most sensitive, the ileum the next, and the right colon the least. With the dose of 1.0 µg per kg, motility indexes of these three portions were entirely of one accord. With a greater dose than 1.0 µg per kg, the responsive order was reversed as compared with that with the lesser. The response of the left colon, with each dose from 0.05 to 0.25 µg per kg, was slightly lesser than that of the jejunum, but stronger than those of the ileum and right colon. To each dose from 0.5 to 2.0 µg per kg, the left colon was very strongly responsive

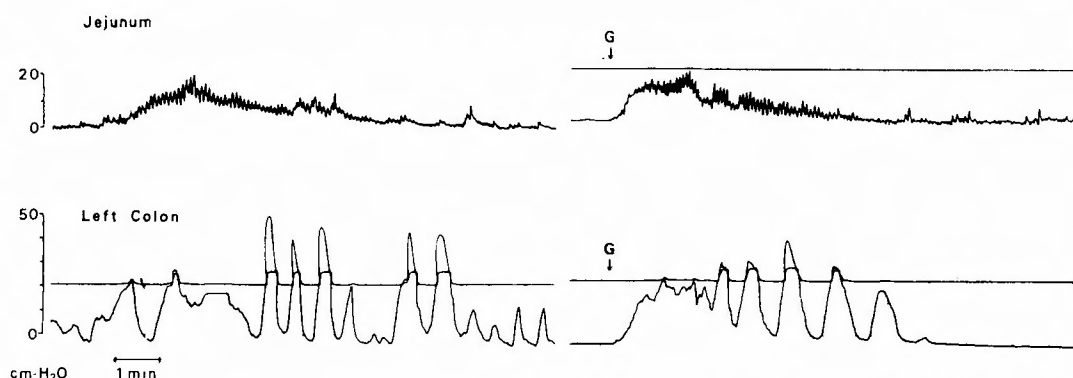


Fig. 6 The effects of test meal instilled into the antrum of the stomach were observed in the jejunum 15 minutes after the instillation, and in the left colon 25 minutes after the instillation. Both wave patterns of the movements produced by the test meal were similar to those provoked by gastrin-like tetrapeptide. G: An intravenous injection of gastrin-like tetrapeptide.

underwent relaparotomy. The gut, severed proximally at the border between the duodenum and jejunum and distally at the rectum as near the anus as possible, was separated, as a whole, at the radix of mesentery, so as to be connected only by superior mesenteric vessels. Perivascular nerves were severed and the adventitia was removed as much as possible. Moreover, by twining a piece of gauze moistened with xylocaine solution around the vessels, denervating effect was assured still more. Using the colon prepared in this manner, the motor activities of the right and left colons were measured in 5 dogs. The motor-effect, provoked by the tetrapeptide, was noticed obviously in all 5 dogs, still after denervation, although the effect reduced in comparison with that before denervation (Fig. 7).

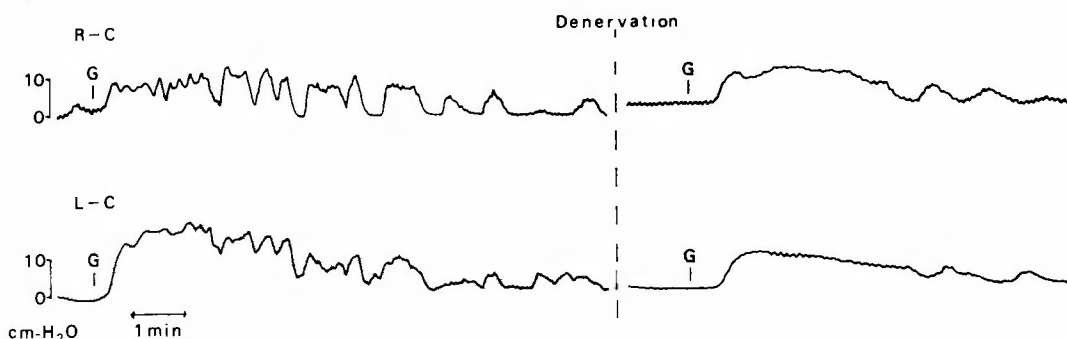


Fig. 7 Influence of denervation on the motor effect of the colon provoked by gastrin-like tetrapeptide. The motor effect was observed even after denervation. G: An intravenous injections of $1.0 \mu\text{g}$ per kg of gastrin-like tetrapeptide. R-C: The right colon. L-C: The left colon.

IV. EFFECTS OF GASTRIN-LIKE TETRAPEPTIDE AND SEROTONIN ON THE MOTILITY OF FREE TRANSPLANTED GASTRIC POUCHES

a) Operative procedure²⁰⁾: The external jugular vein (EJV) and the common carotid artery (CCA) were isolated and cleared of their adventitia in preparation for subsequent anastomoses with the vessels of the transplant. The abdomen was opened, and

the gastric pouch, approximately 10 cm in length, was constructed by outlining it with clamps, excising the portion of the greater curvature and preserving its blood vessels from the splenic vessels, as shown in Fig. 8. A free gastric pouch was transplanted subcutaneously into the neck, and revascularized by end-to-end anastomoses between the common carotid and the splenic arteries and between the external jugular and the splenic veins, respectively, by hand. A Pavlov pouch, which was the same in size as a free gastric pouch, was constructed as a control. Measurement of the movement was performed with the method previously mentioned.

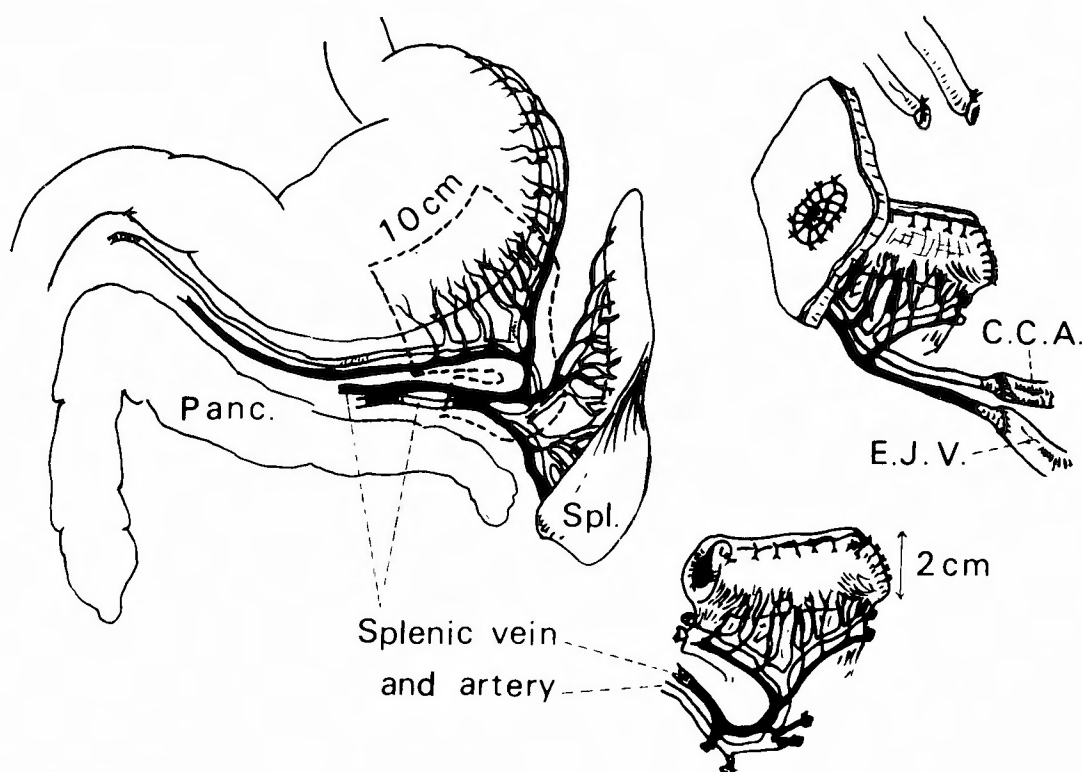


Fig. 8 Diagram of the technique for creating and transplanting a gastric fundic pouch.

b) Result : To each dose of the tetrapeptide from 0.01 to 0.25 μg per kg, the free transplanted gastric pouch was more sensitive than the Pavlov pouch. In the former, the motor effect was observed in an extremely low concentration of 0.01 μg per kg, while in the latter, it was not observed with a lesser dose than 0.05 μg per kg. With each dose from 0.25 to 2.0 μg per kg, the motor effect in the former was lesser than the latter (Fig. 9, 10).

To each dose of serotonin creatinine sulphate from 0.5 to 32.0 μg per kg, the free transplanted gastric pouch was always more sensitive than the Pavlov pouch. In the former, the increased activity was found with 1.0 μg per kg, while, in the latter, it was not observed with a lesser dose than 8.0 μg per kg (Fig. 11, 12).

V. CLINICAL CASES

Case 1. K. F., a 25-year-old woman, cicatricial stenosis of the esophagus: Distal gastrectomy (B II) was previously performed. The right-half colon including the terminal ileum, nourished by middle colic vessels, was raised up antethoracically and subcutaneously. Esophagoileostomy was performed and the transverse colon was anastomosed to an efferent loop of the jejunum. In this case, in spite of no disturbance of passage of a contrast medium through the alimentary tract on X-ray examination after the operation, the contrast medium showed a tendency to stagnate in the substitutive esophagus, that is, the right-half colon.

Case 2. I. A., a 43-year-old woman, cancer of the mid-thoracic esophagus: Distal gastrectomy (B II) was previously performed for gastric ulcer. Two-stage operation for esophageal cancer was performed. As the 1st-stage operation, subtotal resection of the thoracic esophagus and construction of an esophageal fistula in the neck and a gastric fistula were performed. As the 2nd-stage, the right-half colon including the terminal ileum was raised up antethoracically and subcutaneously, and esophagoileostomy was performed. The transverse colon was anastomosed to the gastric remnant. In this case, in spite of no disturbance of passage after the operation, foodstuff showed a tendency to stagnate in the right-half colon. (Photos 1, 2, 3, 4).

Case 3. T. A., a 59-year-old woman, cancer of the mid-thoracic esophagus: Distal gastrectomy (B II) was performed for gastric ulcer. Two-stage operation for esophageal cancer was performed. The 1st-stage operation was performed as in Case 2. As for the 2nd, almost the whole length of the transverse colon including the first part of the descending colon, nourished by the inferior mesenteric vessels, was raised up antethoracically and subcutaneously, and esophago-transversostomy was performed. The descending colon was anastomosed to the gastric remnant. In this case too, in spite of no disturbance of passage after the operation, foodstuff showed a tendency to stagnate in the raised colon (Photos 5, 6).

Case 4. T. H., a 17-year-old woman, cicatricial stenosis of the esophagus: The right-half colon including the terminal ileum was raised up antethoracically and subcutaneously. Bypass operation was performed by esophagoileostomy and anastomosis between

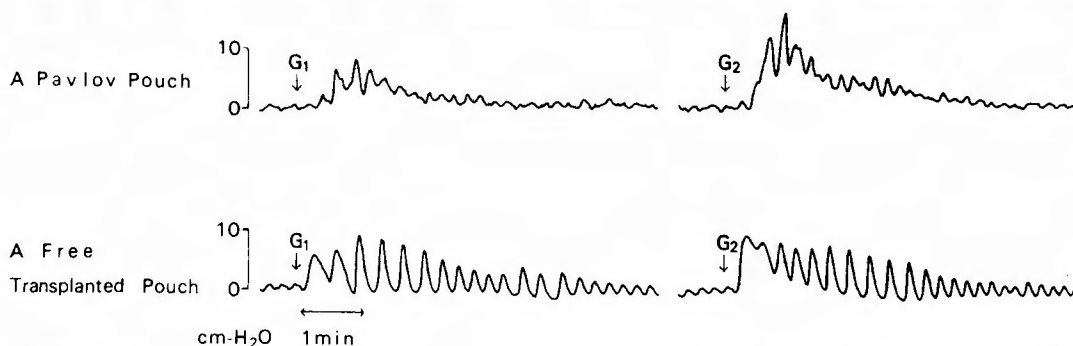


Fig. 9 The effects of a rapid intravenous injection of gastrin-like tetrapeptide, in some doses, on the motility of a free transplanted gastric pouch and a Pavlov pouch. G_1 : $0.1 \mu\text{g}$ per kg, G_2 : $0.25 \mu\text{g}$ per kg of gastrin-like tetrapeptide.

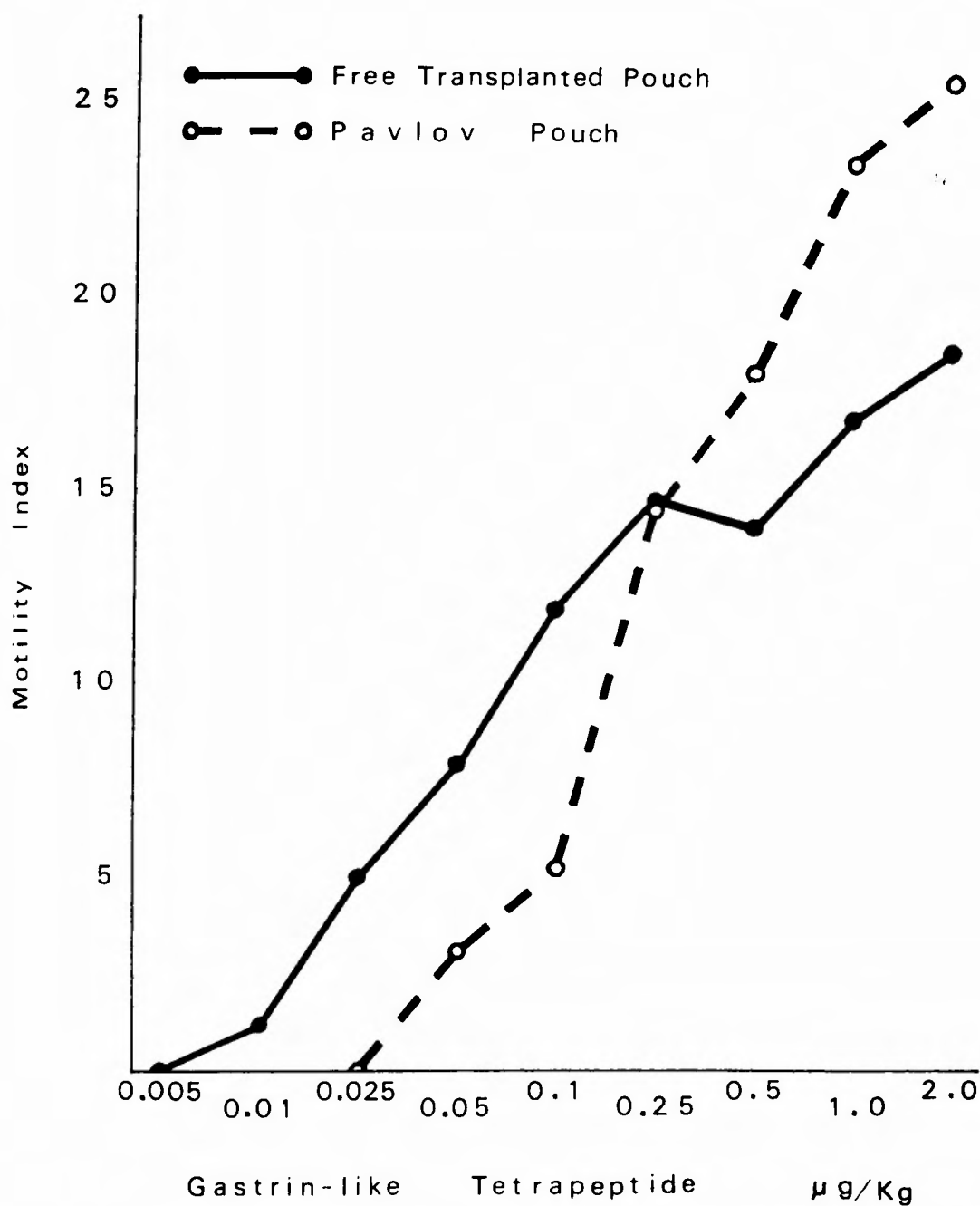


Fig. 10 Dose-response curves for the motility of a free transplanted gastric pouch and a Pavlov pouch in response to gastrin-like tetrapeptide.

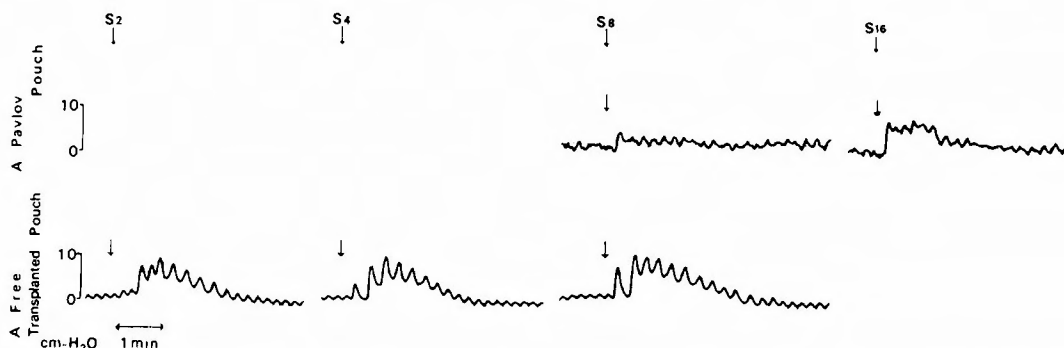
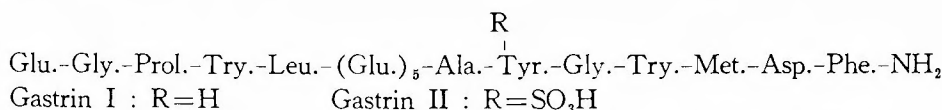


Fig. 11 The effects of a rapid intravenous injection of serotonin, in some doses, on the motility of a free transplanted gastric pouch and a Pavlov pouch. S_2 : 2.0 μg per kg, S_4 : 4.0 μg per kg, S_8 : 8.0 μg per kg, S_{16} : 16.0 μg per kg of serotonin creatinine sulphate.

the transverse colon and an anterior wall of the stomach. In this case, a favorable passage of foodstuff was observed on the raised colon (Photos 7, 8).

VI. DISCUSSION

It was decided by GREGORY and TRACY's analysis¹⁵⁾ that gastrin is in the form of polypeptide. They refined two pure active polypeptides, that is, gastrin I and II from the extract of canine and hog gastric mucosas. Then, it was clarified by GREGORY¹³⁾ that hog gastrin I and II are heptadecapeptide amides which have the following chemical structures:



Chemical structures of human gastrin I and II were decided by BENTLEY⁷⁾ and they were synthesized by BEACHAM¹⁾. In human gastrin, methionine is substituted for the fifth leucine in the chemical structure of hog gastrin mentioned above.

Early studies on the effects of gastrin on the gastrointestinal motility by BLAIR and his colleagues⁸⁾ clarified that intravenous injection of the extract from the antrum into anaesthetized cats not only stimulated gastric secretion, but also produced a strong "pressor effect" on the stomach and upper small intestine. GREGORY and TRACY¹⁶⁾ similarly showed that in conscious dogs, rapid intravenous injections of small quantities of gastrin I and II caused a prompt and powerful spasm of the gastric musculature, and a prompt sustained spasm or rapid series of vigorous contractions in the small intestine. BENNETT⁵⁾ studied on the effects of gastrin II on isolated strips of the stomach, small intestine, and colon of experimental animals and found that the most sensitive tissue was the small intestine. SMITH and HOGG³⁶⁾ examined the effect of gastrin II on the motility of the human gastrointestinal tract, and showed that it had a readily demonstrable motor effect on the small intestine and colon, and suggested that gastrin is a factor which controls the intestinal motility in man, but in doses which were greater than that required to provoke maximal secretion. NEELY³³⁾ showed that in anaesthetized cats an approximately equal effect on the small intestine and colon was observed in response to the administration of

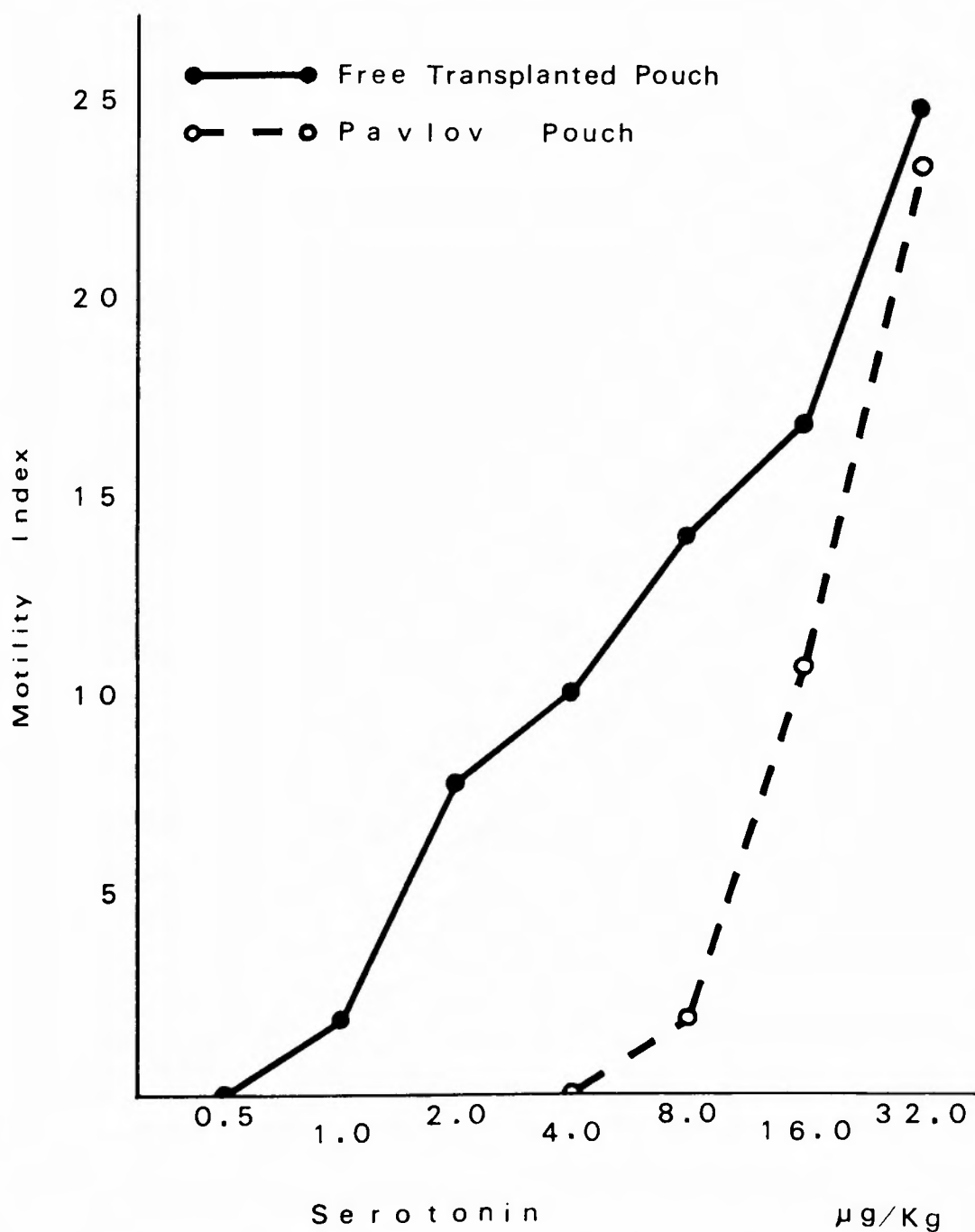


Fig. 12 Dose-response curves for the motility of a free transplanted gastric pouch and a Pavlov pouch in response to serotonin.



Photo 1 A preoperative roentgenogram of Case 2 revealed cancer of the mid-thoracic esophagus.

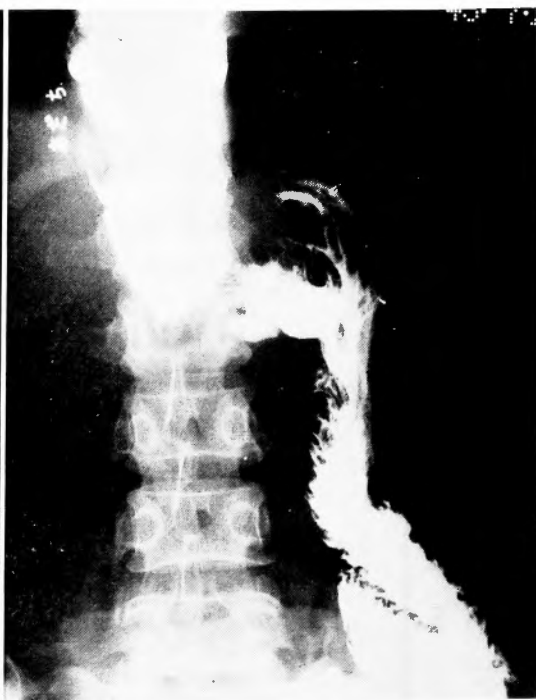
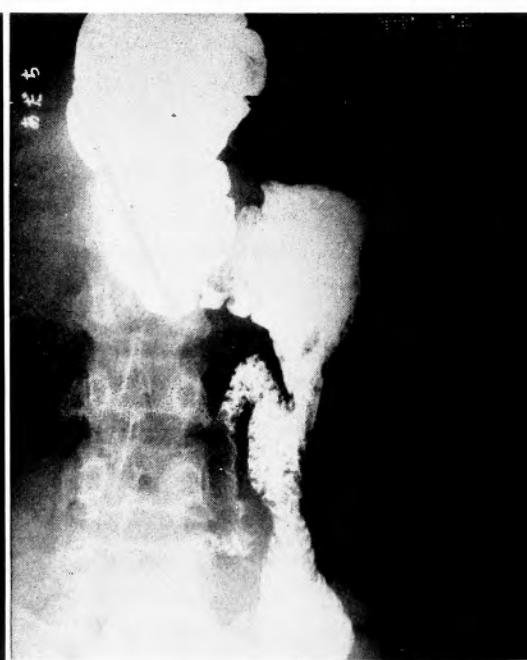


Photo 2 Using a pedunculated right colonic tube, esophageal reconstruction was performed. In this case (Case 2), the patient had undergone distal gastrectomy previously, and the raised colonic tube showed a tendency to stagnate a contrast medium without organic disturbance of passage.



Photos 3, 4 In Case 2, the raised colonic tube showed the same tendency still one year after operation.

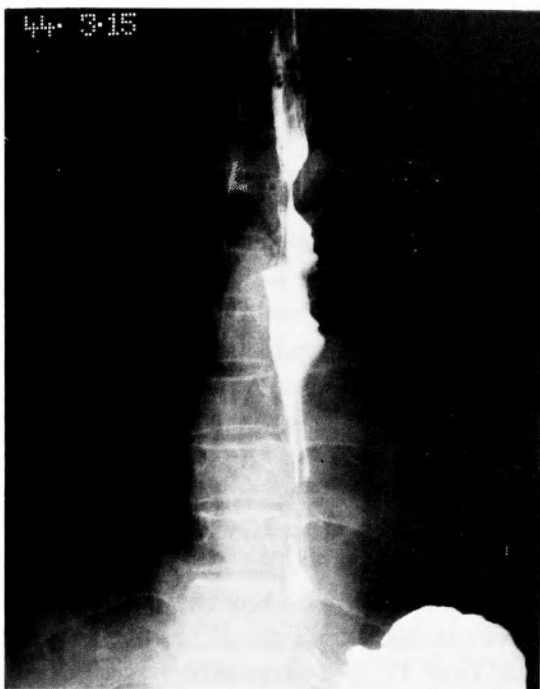


Photo 5 A preoperative roentgenogram of Case 3 revealed cancer of the mid-thoracic esophagus.



Photo 6 Using a pedunculated left colonic tube, esophageal reconstruction was performed. In this case (Case 3), the patient had also undergone distal gastrectomy previously, and the raised colonic tube showed the similar tendency as in Case 2, to stagnate a contrast medium after operation.

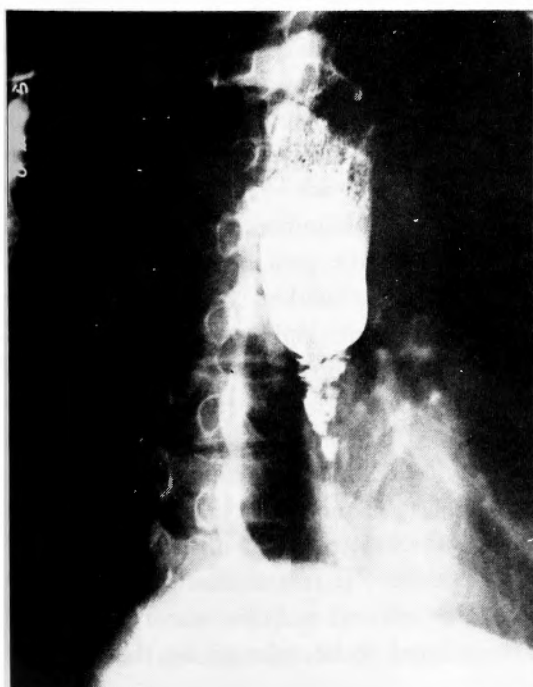


Photo 7 A preoperative roentgenogram of Case 4 revealed cicatricial stenosis of the esophagus.

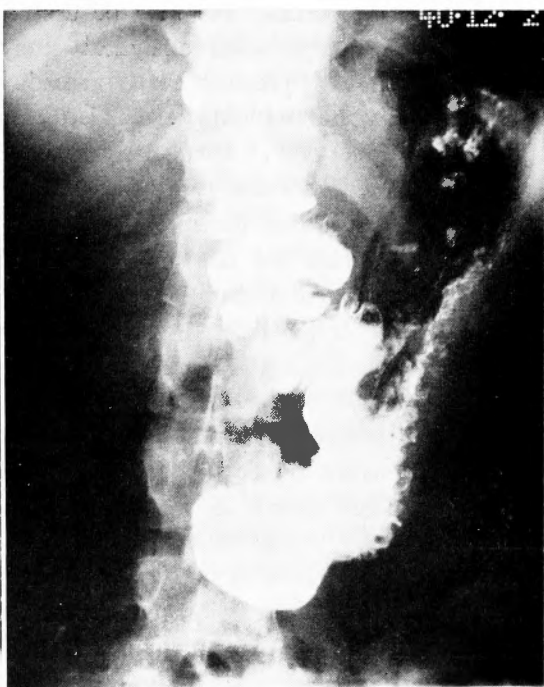


Photo 8 Using a pedunculated right colonic tube, bypass operation was performed. In this case (Case 4), the raised colonic tube showed a favorable motility.

gastrin, and a lesser one on the stomach was observed. TRACY and GREGORY³⁹⁾, who studied on the comparison between physiologically active gastrin-like peptides and natural gastrin, showed that C-terminal tetrapeptides exert all properties that natural gastrin possesses except that they have a kind of inhibitory action on the motor response of the stomach in dogs. However, in the study using I. C. I. 50, 123 (pentapeptide), LOGAN and CONNELL²⁶⁾ observed marked motor response to gastrin in the colon of man, but could see no motor effect in the small intestine. NEELY³⁸⁾ obtained also a similar result, that the colon responded to I. C. I. 50, 123 administered in anaesthetized cats, but there was no effect in the small intestine.

CODE and his colleagues⁹⁾, the MAYO school, described movements of the alimentary tract with the rubber balloon method and classified wave patterns recorded into four types as follows: Type I wave: a small amplitude of the contraction, a short duration time without a change of tonus. Type II wave: an accumulation of two or three Type I waves, a longer periodic time and a larger amplitude of the contraction. Type III wave: a marked change in base line pressure, an accumulation of two or more Type II waves. Type IV wave: a considerable powerful contraction which occurs solitarily once every few minutes and has a duration time beyond one minute. It has been mentioned that in the large intestine, there are Type I, Type II, Type III, and Type IV; Type I, Type II and Type III are nonpropulsive waves but Type IV is a propulsive wave, and that in the small intestine, there are only Type I and Type III, Type I is a nonpropulsive wave, but Type III is a propulsive. It is significant to characterize motorial properties of the gut by measuring changes of its intraluminal pressure. However, as standardized methods for measuring the movement of the gut quantitatively have not been established, various kinds of methods have been used by each investigator. A way, used usually, of dealing with data is to compare the highest intraluminal pressure of the gut. Although this method is concise and may be useful for a certain kind of study, it is rough and inappropriate for a detailed analytical study. Recently, a method of integrating the intestinal intraluminal pressure curve recorded is used as a dynamic expression of the intestinal motility and with this method, the motor effect of the gut can be assayed as absolute kinetic energy³²⁾. Particularly when the effect of a drug is examined, using this method, a more exact analysis can be made, although there are various methods for the actual survey. Motility index, to which the author gives a definition, has been considered the most appropriate for this purpose. In the author's study pentapeptide was not used, but tetrapeptide. Administration of gastrin-like tetrapeptide in dogs has provoked an increased activity of peristalsis in the stomach, jejunum, ileum, right colon and left colon. Furthermore, according to CODE's classification of wave pattern, the bowel movement of the small intestine and colon, provoked by the tetrapeptide, has been classified as peristalsis from which propulsion of intestinal contents results. It has been found that there is a correlation between the intensity of the motility provoked and doses of the tetrapeptide, and dose-response curves, as shown in Fig 5, has been obtained. It is said that gastrin distributes chiefly in the antrum of the stomach, but does not exist in the corpus. There is a report¹⁷⁾ that there is but little gastrin in the cardia. It is said that there is a much lower activity of gastrin in the duodenum than in the antrum, and the activity reduces as it recedes from the pylorus¹²⁾. Gastrin is considered to be released by the following

factors : (1) neural factor - vagal stimulation, (2) mechanical factor - distention of gastric wall of the antrum by food, and (3) chemical factor - meat extract, peptone, amino acids, alcohols, etc¹⁾³⁾²¹⁾³⁴⁾⁴⁰⁾⁴¹⁾. Usually, gastrin is released chiefly by ingestion, in addition, by various combinations of factors described above.

Scrutinizing the dose-response curve obtained from the author's experiment, it has been understood that as a gastrin concentration in blood increases gradually with gastrin released from the antrum after ingestion, first, the jejunum causes its increased activity, and then the peristalsis induces in the ileum and right colon, in this order. On the other hand, it has been shown that the peristalses of the small intestine and colon, induced after instillation of test meal into the antrum of the stomach, are similar to those provoked by the tetrapeptide. These results seem to have suggested that gastrin has a certain significance as a humoral factor which controls the motor function of the gut. The extremely strong response of the left colon has made it presumable that gastrin may participate in the so-called gastrocolic response¹⁰⁾²⁵⁾²⁶⁾. LOGAN has stated that gastrin plays a role as a mediator of the gastrocolic response. However, this substance is not the sole, but pitresin and glucagon possess a possibility of participating also. Based on their experimental results using pentagastrin, MISIEWICZ and his colleagues denied the role of gastrin as a mediator of the gastrocolic response and have taken a serious view of participation of serotonin³⁰⁾.

BENNETT⁵⁾ persisted that as to the intestinal motility gastrin acts on the postganglionic parasympathetic nerves and the contraction produced by gastrin is caused by the release of acetylcholine. However, NEELY³³⁾ observed that gastrin maintained its effect in cats which were atropinized, and moreover administered α -, and β -adrenergic blockades, although the effect of gastrin was abolished in only atropinized cats, and stated that gastrin acts without release of acetylcholine. Because motor response of the denervated gastric pouch and colon to the tetrapeptide was observed in the author's experiments, it must be considered that gastrin acts on parasympathetic ganglia or postganglionic fibers, or directly on smooth muscle. Judging from the experimental results of BENNETT and NEELY, because premedication of atropine intercepted the effect of gastrin completely or partially, a direct action on smooth muscle is difficult to consider. Therefore, it has been presumed that there is some other factor which mediates between gastrin and smooth muscle. Judging from the dose-response curve in comparison between a free transplanted gastric pouch and a Pavlov pouch, the former, which was denervated, responded to gastrin in a much lower concentration than the latter. This result is very interesting in view of CANNON's law that the terminal organ, after denervation, acquires the supersensitivity to a chemical transmitter.

Serotonin is released from the intestinal wall by its distension or ischemia. A free transplanted gastric pouch responded more markedly to serotonin than a Pavlov pouch. This has shown that serotonin possesses the possibility of controlling the motor-function of a free transplanted gastric pouch humorally.

GROSSMAN¹⁸⁾ considered that stimulation of gastric motility by gastrin was a "pharmacological" effect and not of "physiological" significance. However, MIKOS and VANE²⁸⁾ reported that hamster stomach and descending rat colon were contracted by doses of gastrin similar to those required by the bullfrog gastric mucosa for its acid secretion. BENNETT⁶⁾ found that gastrin stimulated human isolated gastric muscle in doses as low as 0.05 μ g

per ml. Therefore, it has been considered that bowel movement in response to gastrin is of physiological significance. KONTUREK²³⁾ showed that the subcutaneous dose of gastrin II required for maximal acid secretion from the vagally innervated dog's stomach is 8 μ g per kg. TRACY³⁹⁾ stated that the power to stimulate acid secretion by subcutaneous injection of the tetrapeptide appeared to be about one-fifth that of gastrin on a simple weight basis. Therefore, the dose of gastrin used in this experiment, in spite of intravenous injection, may be considered enough to be within physiological limits.

In 1942, UVNÄS propounded the hypothesis that vagal stimulation releases gastrin from the antrum, and also that the cephalic phase of gastric acid secretion is controlled by a neurohumoral mechanism in which gastrin from the antrum plays a major role. These were confirmed by MAUNG PE THEIN and SCHOFIELD²⁷⁾ in 1959. It was considered that the vagal release of gastrin from the antrum, elicited by sham feeding, is mediated by a mechanism other than increased motor activity. This mechanism was assumed to consist of a direct nervous excitation of the gastrin-releasing cells via the efferent vagal pathways. On the other hand, vagotomy reduces markedly the gastric response to gastrin-stimulation. ANDERSSON clarified that vagotomy produced a significant reduction of both maximal and submaximal levels of gastric secretion in response to gastrin. The fact that gastrin requires vagally innervated cells for optimal activity, seems not only concerned with the secretion, but also the motor-effect of gastrin. A phenomenon, that increasing hydrogen ion concentration in the pyloric antrum inhibits the release of gastrin, was elucidated by WOODWARD and his colleagues⁴⁰⁾. Namely, it has been generally accepted that a powerful inhibition is exerted against all stimuli releasing gastrin from the pyloric antrum when the pH in the adjacent lumen is lowered to the region of 3.0 or less¹⁹⁾.

Bearing matters described above in mind the author scrutinized our clinical cases of esophageal reconstruction. In Case 1, gastrin is not released because there is no antrum and no passage of food through the stomach and duodenum, although vagal innervation is maintained due to the unenforcement of esophagectomy. In Cases 2 and 3, gastrin is not released because of vagotomy caused by esophagectomy and of no antrum. Although colonic tubes, utilized in Cases 2 and 3 for esophageal reconstruction, were different respectively in sort and in the predominancy of vagal innervation, in both cases after the operation a contrast medium showed a tendency to stagnate in the raised colon in spite of no disturbance of passage. In Case 4, the motor-function of the raised colon seemed favorable because vagal innervation, the antrum and storage of food in the stomach were preserved by reason of bypass operation.

These clinical observations have suggested that the motor-function of pedunculated colonic tubes of which autonomic nerves are severed partially, and which are raised up to an abnormal antethoracic and subcutaneous position, is controlled by gastrin to some extent. If esophagectomy is added to the operation in Case 1, vagotomy is accompanied as a matter of course. It is thought to be logical that prolonged influence of gastrin is expected because reduced acid secretion by vagotomy diminishes an inhibition of gastrin-release caused by acidification of the antrum, although reduced vagal gastrin-release and decreased sensitivity of a target organ to gastrin diminish the influence of gastrin. In clinical cases enumerated here, the right-half colons were used. However, considering the gastrin mechanism, utilization of the left colon must be also considered, in which the innervation of pelvic nerve

as parasympathetic is predominant.

VII. CONCLUSION

Using gastrin-like tetrapeptide, the author has studied experimentally the role of gastrin as a humoral factor which may control the motor-function of gastric and intestinal tubes for esophageal reconstruction.

1) Intravenous injections of gastrin-like tetrapeptide into dogs increased the activity of bowel movement in the jejunum, ileum, right colon and left colon. From the analysis of the wave patterns, the bowel movements provoked by the tetrapeptide have been regarded as peristalsis from which propulsion of intestinal contents results. To a lesser dose than $1.0 \mu\text{g}$ per kg, except the left colon, the jejunum was the most sensitive and the responses reduced in the ileum and the right colon in this order. This result has made it presumable that gastrin may participate in the mechanism by which writhing movements of the bowel, after ingestion, spread from an upper portion to a lower portion. Extremely strong responses, shown in the left colon, have indicated that gastrin may participate in the so-called gastrocolic response.

2) The wave patterns, which were observed in the jejunum and the left colon after instillation of test meal into the antrum of the stomach, were similar to those induced following the intravenous injection of the tetrapeptide.

3) In an acute experiment, the denervated colon was sensitive to the tetrapeptide. In a chronic experiment, a vagally and sympathetically denervated, free transplanted gastric fundic pouch was more sensitive to the tetrapeptide than a vagally and sympathetically innervated Pavlov pouch. This has indicated that gastrin is a humoral factor with regard to the bowel movement.

4) There is no systemic experiment with regard to serotonin in this study. However, this drug induced the motor effect in a free transplanted gastric pouch, and a transplanted gastric pouch was more sensitive to serotonin than Pavlov pouch. These have suggested that serotonin may be a humoral factor in the movement of gastrointestinal tract.

5) Considering the gastrin mechanism, the author has scrutinized clinical cases of esophageal reconstruction described above, and has indicated that it is desirable to anastomose a distal end of the pedunculated colonic tubes to the stomach, especially, in bypass operations of the esophagus.

ACKNOWLEDGEMENT

Grateful acknowledgement is made to Prof. Dr. CHUJI KIMURA for his kind guidance, and to Associate Prof. Dr. KOICHI ISHIGAMI for many valuable suggestions and criticisms throughout this investigation. The gastrin-like tetrapeptide used in this experiment was supplied by Eisai Pharmaceutical Company.

The abstract of this paper was presented before the 55th General Meeting of Japanese Society of Gastroenterology, Sendai, April 4, 1969.

REFERENCES

- 1) Andersson, S. and L. Olbe : Inhibition of gastric acid response to sham feeding in Pavlov pouch dogs by acidification of antrum. *Acta Physiol. Scand.*, **61** : 55-64, 1964.
- 2) Andersson, W. R. : Isolation and assay of ovine gastrin. *Nature (Lond.)*, **193** : 1286-1287, 1962.
- 3) Baugh, C. M., T. L. Bravo, J. Barcena and L. R. Dragstedt : Studies on the site and mechanism of gastrin release. *Arch. Surg.*, **76** : 441-446, 1958.

- 4) Beacham, J. : Synthesis of human gastrin I. *Nature (Lond.)*, **209** : 585-586, 1966.
- 5) Bennett, A. : Effect of gastrin on isolated smooth muscle preparation. *Nature (Lond.)*, **208** : 170-173, 1965.
- 6) Bennett, A., J. J. Misiewicz and S. L. Waller : The effect of gastrin and a gastrin-like pentapeptide on human isolated gastrointestinal muscle. *Brit. J. Surg.*, **54** : 232-233, 1967.
- 7) Bentley, P. H. : Structures of human gastrin I and II. *Nature (Lond.)*, **209** : 583-585, 1966.
- 8) Blair, E. L. et al. : A simple method of preparing gastrin. *J. Physiol (Lond.)*, **156** : 11-12, 1961.
- 9) Code, C. F. et al. : Motility of the alimentary canal in man. Review of recent studies. *Am. J. Med.*, **13** : 328-351, 1952.
- 10) Connell, A. M. and C. J. H. Logan : The role of gastrin in gastroileocolic responses. *Am. L. Dig. Dis. (New Series)*, **12** : 277-284, 1967.
- 11) Edkins, J. S. : On the chemical mechanism of gastric secretion. *Proc. Roy. Soc. London.*, **76** : 376, 1905.
- 12) Elwin, C. E. and B. Uvnäs : Distribution and local release of gastrin. Univ. of California Press, Los Angeles, ed. by M. I. Grossman, 69-82, 1966.
- 13) Gregory, H. : The antral hormone. Structure of gastrin. *Nature (Lond.)*, **204** : 931-933, 1964.
- 14) Gregory, R. A. et al. : Isolation of two gastrins from human antral mucosa. *Nature (Lond.)*, **209** : 583, 1966.
- 15) Gregory, R. A. and H. J. Tracy : Constitution and properties of two gastrins extracted from hog antral mucosa. *J. Physiol.*, **169** : 18, 1963.
- 16) Gregory, R. A. and H. J. Tracy : Constitution and properties of two gastrins extracted from hog antral mucosa. *Gut*, **5** : 103-144, 1964.
- 17) Gregory, R. A. and H. J. Tracy : The preparation and properties of gastrin. *J. Physiol.*, **156** : 523-543, 1961.
- 18) Grossman, M. I. : Some aspects of gastric secretion. *Gastroenterology*, **52** : 882-892, 1967.
- 19) Grossman, M. I. et al. : Gastrin. Butterworth & Co. L. T. D., London, 1966.
- 20) Hopkins, D. M. et al. : Experimental replacement of the cervical esophagus. *Arch. Surg.*, **87** : 265-275, 1963.
- 21) Ivy, A. C. and A. J. Javois : Contribution to the physiology of gastric secretion. V. The stimulation of gastric secretion by amino acids. *Am. J. Physiol.*, **71** : 591-603, 1925.
- 22) Komarov, S. A. : Gastrin. *Proc. Soc. Exp. Biol. Med.*, **38** : 514-516, 1938.
- 23) Konturek, S. : Acid response to gastrin and related peptides. *Gastroenterology*, **50** : 650-652, 1966.
- 24) Lim, R. K. S. and P. Mozer : Mechanism of excitation of internal secretion of pylorus and adenteric reflex. *Am. J. Physiol.*, **163** : 730, 1950.
- 25) Logan, G. J. H. : Gastrin as an intestinal activator. *Brit. J. Surg.*, **54** : 297-301, 1967.
- 26) Logan, C. J. H. and A. M. Connell : The effect of a synthetic gastrin-like pentapeptide (I. C. I. 50, 123) on intestinal motility in man. *Lancet*, **1** : 996-999, 1966.
- 27) Maung Pe Thein and B. Schofield : Release of gastrin from the pyloric antrum following vagal stimulation by sham feeding in dogs. *J. Physiol.*, **148** : 291-305, 1959.
- 28) Mikos, E. and J. R. Vane : Effects of gastrin and its analogues of isolated smooth muscle. *Nature (Lond.)*, **214** : 105-107, 1967.
- 29) Misiewicz, J. J., D. J. Holdstock and S. L. Waller : Motor responses of the human alimentary tract to near-maximal infusions of pentagastrin. *Gut*, **8** : 463-469, 1967.
- 30) Misiewicz, J. J., S. L. Waller and M. Eisner : Motor responses of human gastrointestinal tract to 5-hydroxytryptamine in vivo and in vitro. *Gut*, **7** : 208-216, 1966.
- 31) Morley, J. S. : Structure-function relationships in the active C-terminal tetrapeptide sequence of gastrin. *Nature (Lond.)*, **207** : 1356-1359, 1965.
- 32) 中山恒明, 他 : 胃アトニーの運動量による分類とその臨床的意義. *外科*, **24** : 1203-1208, 1962.
- 33) Neely, J. : Comparison of the effects of a gastrin extract and a synthetic pentapeptide on gastrointestinal motility in the cat. *Gut*, **8** : 242-248, 1967.
- 34) Nyhus, L. M. et al. : The control of gastrin release: An experimental study illustrating a new concept. *Gastroenterology*, **39** : 582-589, 1960.
- 35) Robertson, C. R., et al. : Release of gastrin in response to bathing the pyloric mucosa with acetylcholine. *Am. J. Physiol.*, **163** : 27-33, 1950.
- 36) Smith, A. N. and D. Hogg : Effect of Gastrin II on the motility of the gastrointestinal tract. *Lancet*, **1** : 403-404, 1966.
- 37) 嶋田俊恒 : 腸管遊離移植に関する研究 (特に移植された腸管の機能について). *日外会誌*, **67** : 495-514, 1966.
- 38) 島本暉明 : Gastrin. *ホルモンと臨床*, **15** : 375-379, 1967.
- 39) Tracy, H. J. and R. A. Gregory : Physiological properties of a series of synthetic peptides structurally related to gastrin I. *Nature (Lond.)*, **204** : 935-938, 1964.

- 40) Woodward, E. R. et al. : The physiology of the gastric antrum ; experimental studies on isolated ant-
rum pouches in dogs. *Gastroenterology*, **27** : 766-785, 1954.
41) Woodward, E. R. et al. : Alcohol as a gastric secretory stimulant. *Gastroenterology*, **32** : 727-737, 1957.

和 文 抄 録

食道再建用有茎および完全遊離移植胃腸管の 運動機能に対する体液性支配因子について

京都大学医学部外科学教室第2講座（指導：木村忠司教授）

行 森 清 治

近年、細小血管吻合法の進歩によつて完全遊離腸管による食道再建術も数多く行なわれ、この術式の臨床的価値は確立されたと云うことができよう。しかしながらその基礎的研究は未だ充分とは云いがたく、ことに完全遊離移植後の腸管運動機能を支配する体液性因子については、その本態は究明されていない。著者はこの点に関するガストリンおよびセロトニンの役割を検討すべく、ガストリン様テトラペプチドおよびセロトニンを用い、犬において次の実験的研究を行なつた。

1) 腸管各部位の運動機能に対するガストリン様テトラペプチドの効果。

2) 胃前庭部への試験食の注入の空腸および結腸左半に対する運動効果。

3) 結腸においてガストリン様テトラペプチドによつて惹起される運動効果に対する除神経の影響。

4) ガストリン様テトラペプチドおよびセロトニンの完全遊離移植胃腸の運動機能に対する効果。

以上の各効果を小ゴム・バルーン法によつて腸管運動の内圧曲線を描記せしめて観察した。運動波形については Code の分類にしたがつて、運動の程度については、内圧曲線を積分することによつてえられた運動指数をもつて定量的に解析した。

これらの結果、1) ガストリン様テトラペプチドの静注は犬の空腸、回腸、結腸右半および左半の運動亢進を惹起した。運動波形の分析からテトラペプチドによる腸管運動は腸内容を推進せしめる輸送波とみなされた。1.0 $\mu\text{g}/\text{kg}$ 以下の小量投与では結腸左半を除いて空腸が最もよく反応し、回腸、結腸右半の順に反応が低下した。この成績は食物摂取によつて惹起される蠕動亢進が上部腸管から下部腸管へ伝播する機序にガストリンが関与することを推定せしめるものである。結腸左半において、とくに強い反応がみられたこ

とは、いわゆる胃結腸反射にガストリンが関与していることを示している。

2) 試験食を胃前庭部に注入した際にみられる空腸および結腸左半の運動波形はテトラペプチドによるそれらと類似していた。

3) 急性実験的に除神経された結腸においてもテトラペプチドによる運動効果がみられた。慢性実験において、交感神経的にも、迷走神経的にも除神経された完全遊離移植胃腸は全く除神経されていないパブロフ胃嚢に比してガストリン様テトラペプチドに対して鋭敏に反応した。このことはガストリンが胃および腸管運動機能に關与する体液性支配因子であることをさらに明確に示している。

4) セロトニンについては、本研究において系統的な実験はなされていないが、それは完全遊離移植胃腸に対して運動効果を示し、パブロフ胃嚢に対する効果と比較すると、前者は後者より強く反応した。このことはセロトニンもまた体液性支配因子となりうる可能性を示している。

5) 以上の実験によつて明らかにされたガストリン機構を考慮して、有茎結腸管を用いて胸廓前食道再建を施行した臨床例を検討してみると、既往に末梢側胃切除術をうけたため、内因性ガストリンの分泌の乏しいあるいは全くないと考えられる症例では、術後、器質的通過障害がみられないにもかかわらず、挙上結腸内に内容が停滞する傾向を認めた点から、ガストリンは食道再建用有茎結腸管の運動機能を支配する一液体性因子とみなすことができよう。この観点から、有茎結腸管を用いて食道を再建する場合、挙上結腸の運動機能を好都合に保持させるためにはその末梢側端はなるべく胃に吻合することが望ましいことを指摘したい。