Tohoku J. exp. Med., 1983, **139**, 205–215

Disturbances of the Alimentary Tract Motility and Hypermotilinemia in the Patients with Diabetes Mellitus

CHIYUKI NAKANOME, HIROAKI AKAI, MICHIO HONGO, NOBUYUKI IMAI, TAKAYOSHI TOYOTA, YOSHIO GOTO, FUMINOBU OKUGUCHI* and KANJI KOMATSU†

*Third Department of Internal Medicine, Tohoku University School of Medicine, Sendai 980, *Tohoku Teishin Hospital, Sendai 980 and †Yuri General Hospital, Honjo 015*

NAKANOME, C., AKAI, H., HONGO, M., IMAI, N., TOYOTA, T., GOTO, Y., OKUGUCHI, F. and KOMATSU, K. *Disturbances of the Alimentary Tract Motility and Hypermotilinemia in the Patients with Diabetes Mellitus.* Tohoku J. exp. Med., 1983, **139** (2), 205–215 —— Lower esophageal sphincter pressure (LESP), gastric emptying, small bowel transit time and plasma motilin levels were measured in diabetics and normal subjects in order to investigate the disturbances of the alimentary tract motility and the participation of motilin in these motility disorders. Hypermotilinemia was observed in all diabetics with or without autonomic neuropathy. Low response of LESP to tetragastrin found in diabetics with autonomic neuropathy could not be explained by motilin. Gastric emptying was highly correlated with fasting plasma motilin levels and a significantly accelerated gastric emptying observed in diabetics without complications or diabetics with diarrhea was considered to be due to hypermotilinemia. On the contrary, no significant correlation was observed between small bowel transit time and plasma motilin levels, suggesting no participation of endogenous motilin in the regulation of small bowel transit. —— lower esophageal sphincter pressure; gastric emptying; small bowel transit time; motilin; diabetic autonomic neuropathy

Disturbances of the alimentary tract motility have been observed frequently in the patients with diabetes mellitus. Swallowing disorder in diabetics with neuropathy-gastroenteropathy (Mandelstram et al. 1969), significantly fast gastric emptying of a liquid meal in diabetics without complications (Dotevall 1961), and delayed small bowel transit time in diabetics with autonomic neuropathy (Scarpello et al. 1976) have been reported to date. On the other hand, motilin, discovered by Brown et al. (Brown 1967; Brown et al. 1972), is well known to affect lower esophageal sphincter (Itoh et al. 1976), gastric emptying (Christofides et al. 1979, 1981) and small bowel transit time (Ruppin et al. 1976). Motilin has been considered to be one of the most important gut hormones affecting the

Received for publication, May 10, 1982.

Mailing address for requests of reprints: C. Nakanome, Yuri General Hospital, 38 Higashi-machi, Honjo, Akita 015, Japan.

alimentary tract motility. In this study, we have measured lower esophageal sphincter pressure (LESP), gastric emptying, small bowel transit time and plasma motilin concentrations in diabetics and normal subjects in order to investigate the participation of motilin in the disturbances of the alimentary tract motility in diabetics.

Materials and Methods

Plasma motilin concentrations in the fasting state. Fasting plasma motilin concentrations were measured in 42 diabetics (mean age 41 years, range 15–74 years) and 42 normal subjects (mean age 33 years, range 19–42 years). Diabetics consisted of 15 diabetics without diabetic complications (mean age 47 years, range 38–66 years), 7 with diabetic diarrhea (mean age 27 years, range 18–33 years), 3 with gastroparesis diabeticorum (mean age 44 years, range 35–50 years), 7 with autonomic neuropathy involving orthostatic hypotension, neurogenic bladder, decreased sweating and ejaculatory dysfunction, but without diarrhea or gastroparesis (diabetics with autonomic neuropathy (others)), (mean age 39 years, range 19–51 years) and 10 with diabetic nephropathy (mean age 46 years, range 18–64 years).

LESP, gastric emptying, small bowel transit time and plasma motilin concentrations. Out of diabetics and normal subjects mentioned above, 11 diabetics without complications (mean age 45 years, range 38–66 years), 7 with diabetic diarrhea, 3 with gastroparesis, 7 with autonomic neuropathy (others), 4 with nephropathy (mean age 43 years, range 18–60 years) and 14 normal subjects (mean age 24 years, range 19–25 years) participated in the study of the relationship between LESP, gastric emptying, or small bowel transit time and plasma motilin concentrations. However, the measurements of LESP were not carried out in diabetics with gastroparesis or with nephropathy. Therefore, the data of LESP consisted of the results in diabetics without complications, diabetics with autonomic neuropathy (others) and normal subjects. All of the diabetics with diarrhea showed a severe diarrhea with concomitant approximately ten times of bowel movement a day. The diagnosis of gastroparesis diabeticorum was made according to Malagelada's criteria (Malagelada et al. 1980). All of the diabetics except diabetics with nephropathy showed the normal renal function.

Measurement of plasma motilin concentrations in the fasting state in diabetics and normal subjects. Plasma motilin concentration was determined at 10 min intervals for 120 min after an overnight fast, as motilin is known to fluctuate in the fasting state. Correlations between gastric emptying or small bowel transit time and the following factors of plasma motilin were investigated: fasting mean motilin concentration (FMMC, pg/ml), the mean concentration of plasma motilin for 120 min in the fasting state, fasting integrated motilin concentration (FIMC, ng·min/ml), motilin area calculated from the area circumscribed by motilin curves for 120 min in the fasting state, postprandial mean motilin concentration (PMMC, pg/ml), the mean concentration of plasma motilin for 120 min after the ingestion, postprandial integrated motilin concentration (PIMC, ng.min/ml), and motilin area calculated from the area circumscribed by motilin curves for 120 min after the ingestion.

Measurements of LESP and plasma motilin concentrations. LESP was measured with a station pull through method as previously described (Nagasaki et al. 1977). Subjects were examined in the supine position after an overnight fast. After the measurement of the resting LESP, a bolus injection of tetragastrin 0.5 μg/kg was carried out and LESP was measured for 30 min after the injection. Blood collections for the determination of plasma motilin concentrations were performed at 10 min intervals for 120 min before the measurement of LESP and 2, 5, 10, 15, 20, 30 min after tetragastrin injection, because motilin is known to fluctuate in the fasting state.

Measurements of gastric emptying, small bowel transit time and plasma motilin concentrations. Gastric emptying and small bowel transit time were measured simultaneously on

different days before or after the measurement of LESP. After an overnight fast, subjects ingested a liquid test meal (protein 9.6 g, fat 4.6 g, carbohydrate 30.0 g, total calorie 212.6 kcal, pH 6.5, osmolarity 750 mOs/liter, 200 ml) containing acetaminophen 1.5 g and lactulose 13 g. Gastric emptying was determined by the acetaminophen method (Heading et al. 1973; Harasawa et al. 1979) and expressed by plasma acetaminophen concentration at 45 min after the ingestion based on the preliminary study that plasma acetaminophen concentration at 45 min after the ingestion was most closely correlated with the half gastric emptying (T1/2) determined by γ-camera (Hitachi EDR 4200) with the use of 99 mTc-DTPA ($r=0.84$, $p<0.01$). Plasma acetaminophen concentration was measured by the method of Routh et al. (1968).

Small bowel transit time was measured by the method of Bond and Levitt (1975) using 13 g of lactulose. Pulmonary hydrogen was collected by the end-expiratory method (Metz et al. 1976) at 10 min intervals after test meal ingestion and measured by a Yanaco Type G 1800-T gaschromatograph (Yanagimoto Co., Kyoto) with argon as a carrier gas (Maruhama et al. 1980). Blood samples for the determination of plasma motilin concentrations were obtained every 10 min for 120 min before and after the ingestion, and collected into tubes containing aprotinin and EDTA and were kept on ice until separation into plasma by centrifugation. Plasma samples were kept frozen at −20°C until assay. Plasma motilin concentration was measured by radioimmunoassay (Shin et al. 1980), The double antibody method was used to separate bound from free hormone. The immunoassay system was sufficiently sensitive to detect 25 pg/ml of plasma motilin. Statistical analysis was carried out by the Student's t-test. p values less than 0.05 were considered to be significant. Results were expressed as the mean±S.E.

Results

Fasting motilin concentrations in diabetics and normal subjects

FMMC and FIMC in diabetics and normal subjects are shown in Fig. 1. FMMC and FIMC in 42 normal subjects were 123±10 pg/ml and 15.2±1.2 ng·min/ml, respectively. FMMC and FIMC in each group of diabetics were significantly greater than the values in normal subjects.

LESP and plasma motilin concentrations in diabetic and normal subjects

In 14 normal subjects, the resting LESP was 26.1±3.5 cmH_2O and LESP rose significantly from the resting value to 48.0±7.1 cmH_2O after the injection of tetragastrin ($p<0.05$, Fig. 2). However, no significant correlation was observed between FMMC, FIMC or basal motilin concentration before the injection of tetragastrin (0 min) and the resting LESP (Fig. 3). Plasma motilin concentrations remained unchanged after the injection of tetragastrin and there was no significant correlation between the response of LESP to tetragastrin and plasma motilin concentrations after the injection of tetragastrin.

The resting LESP and the response of LESP to tetragastrin were normal in diabetics without complications. On the contrary, significantly low responses of LESP to tetragastrin were found in diabetics with diarrhea and in diabetics with autonomic neuropathy (others) (Fig. 2). There was no correlation between the resting LESP or the response of LESP to tetragastrin and plasma motilin concentrations in diabetics.

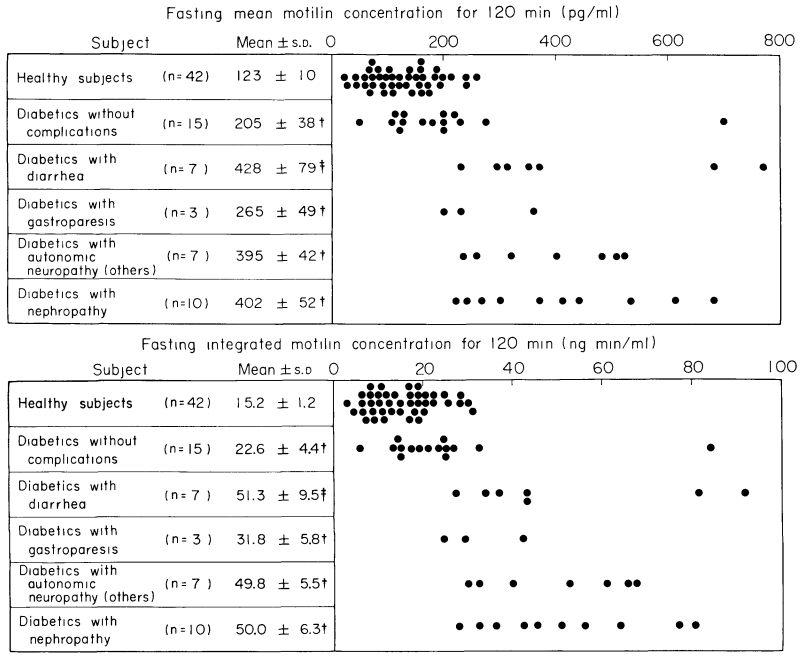

Fig. 1. Fasting mean motilin concentration for 120 min and fasting integrated motilin concentration for 120 min in diabetics and normal subjects. *$p<0.05$, †$p<0.01$, ‡$p<0.001$ vs. normal subjects.

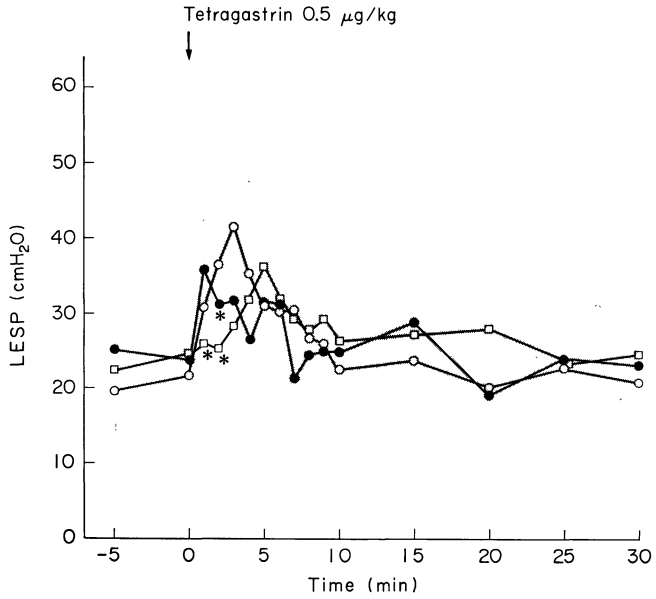

Fig. 2. LESP response to a bolus injection of tetragastrin 0.5 μg/kg in diabetics without complications (○—○), diabetics with diarrhea (●—●), diabetics with autonomic neuropathy (others) (□—□), and normal subjects. Shaded area indicates LESP in 14 normal subjects (mean±S.D.). Symbols are the same as in Fig. 1.

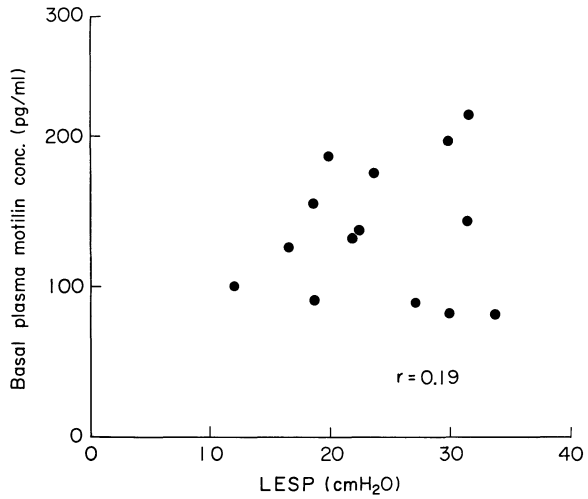

Fig. 3. Relationship of basal motilin concentration and the resting LESP in normal subjects.

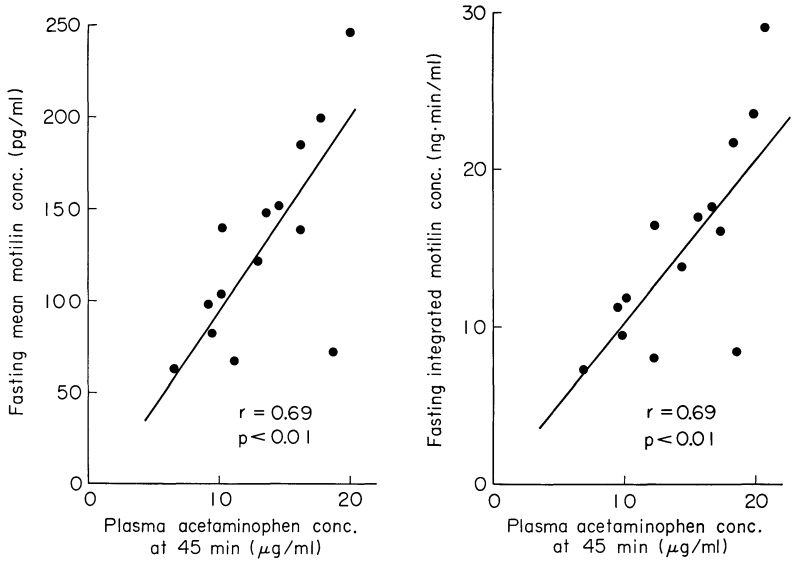

Fig. 4. Relationship of fasting mean motilin concentration, or fasting integrated motilin concentration for 120 min, and plasma acetaminophen at 45 min after ingestion in normal subjects.

Gastric emptying and plasma motilin concentrations in diabetics and normal subjects

A significant positive correlation was observed between plasma acetaminophen concentration at 45 min after the ingestion and FMMC or FIMC (r=0.69, p<0.01; r=0.69, p<0.01) (Fig. 4). Plasma acetaminophen concentration at 45 min after the ingestion in diabetics without complications, 15.7±2.6 μg/ml, was significantly

higher than the value in normal subjects, 13.0±1.2 μg/ml, indicating the significantly accelerated gastric emptying in diabetics without complications. FMMC and FIMC were significantly greater in diabetics without complications, and a significant positive correlation was observed between plasma acetaminophen concentration at 45 min after the injection and FMMC, or FIMC in this group (r=0.82, p<0.01; r=0.82, p<0.01). Diabetics with diarrhea showed a markedly high concentration of plasma acetaminophen concentration at 45 min after the ingestion, indicating the markedly fast gastric emptying, with concomitant high levels of FMMC and FIMC. A significant positive correlation was also found between plasma acetaminophen concentration at 45 min after the ingestion and FMMC or FIMC in diabetics with diarrhea (r=0.86, p<0.01; r=0.86, p<0.01). On the other hand, a significantly low concentration of plasma acetaminophen at 45 min, indicating the significantly delayed gastric emptying, was observed in diabetics with gastroparesis. Gastric emptying in diabetics with neuropathy (others) and diabetics with nephropathy was slower, though insignificantly, than the value in normal subjects (Table 1).

TABLE 1. *Plasma acetaminophen concentration at 45 min after ingestion, small bowel transit time, fasting mean or integrated motilin concentration for 120 min and postprandial mean or integrated motilin concentration*

Subjects	Acetaminophen conc. at 45 min (μg/ml)	Small bowel transit time (min)	Fasting mean motilin conc. (pg/ml)	Fasting integrated motilin conc. (ng·min/ml)	Postprandial mean motilin conc. (pg/ml)	Postprandial integrated motilin conc. (ng·min/ml)
Healthy subjects (n=14)	13.0±1.2	98±11	127± 14	15.3± 1.8	137±14	16.6±1.6
Diabetics without complications (n=11)	16.8±1.0*	89±15	244± 66*	26.9± 7.5*	274±43*	33.2±5.1†
Diabetics with diarrhea (n=7)	21.1±3.2†	40± 8*	428± 79‡	51.3± 9.5‡	359±51‡	41.8±4.2‡
Diabetics with gastroparesis (n=3)	7.7±0.6*	60± 5	265± 49†	31.8± 5.8†	282±24‡	33.1±3.5‡
Diabetics with autonomic neuropathy (others) (n=7)	10.2±1.5	148±18*	395± 42†	49.8± 5.5†	421±49†	58.3±7.4†
Diabetics with nephropathy (n=4)	10.0±1.8	103±29	436±103†	52.3±12.4†	516±67‡	59.7±8.5‡

* p<0.05, † p<0.01, ‡ p<0.001 (vs. normal subject).

Small bowel transit time and plasma motilin concentrations in diabetics and normal subjects

Small bowel transit time was not correlated with any of FMMC, FIMC, PMMC and PIMC (Fig. 5). Diabetics without complications showed the normal small

bowel transit time. Diabetics with diarrhea showed a significantly short small bowel transit time. No correlation, however, was observed between plasma motilin concentrations and small bowel transit time. Small bowel transit time was short in diabetics with gastroparesis, though gastric emptying was markedly

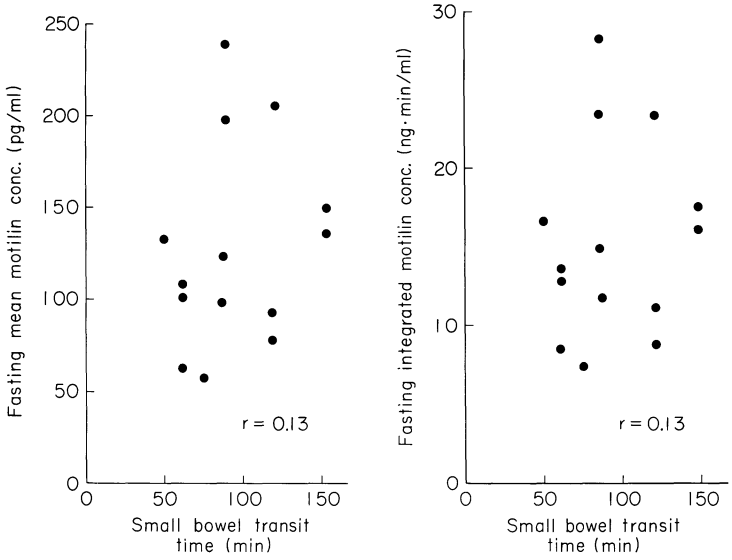

Fig. 5. Relationship of fasting mean motilin concentration, or fasting integrated motilin concentration for 120 min, and small bowel transit time in normal subjects.

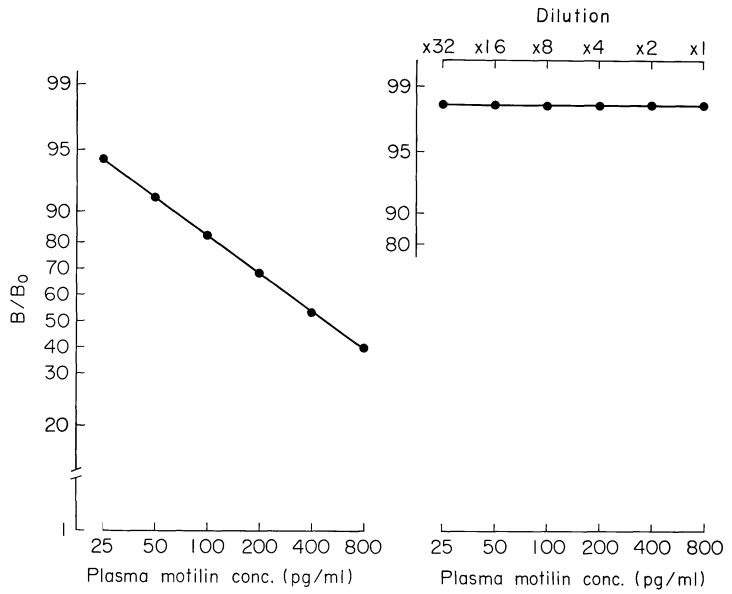

Fig. 6. Comparative immunoreactivities of commercially available insulins in cross reactions with motilin antiserum.

delayed. On the other hand, diabetics with autonomic neuropathy (others) showed a significantly delayed small bowel transit time (Table 1).

Relationship of gastric emptying and small bowel transit time

Correlation of plasma acetaminophen at 45 min after the ingestion and small bowel transit time was investigated in 14 normal subjects. No correlation was observed between them (r=0.13).

Immunoreactive motilin in the commercially available insulins

Immunoreactive motilin in the commercially available insulins was measured in order to investigate the possibility that the commercially available insulins used in diabetics investigated in this study were responsible for hypermotilinemia. No immunoreactive motilin was determined in any of commercially available insulins (Fig. 6).

Discussion

In this study, all of the diabetic patients have been found to show hypermotilinemia, and the disturbances of the alimentary tract motility in diabetics have been shown to be heterogenous. Motilin, as well as other gut hormones, has been considered to be inactivated by the kidney (Shima et al. 1979). However, diabetics investigated in this study except those with nephropathy showed the normal renal function. In addition, no immunoreactive motilin was found in the commercially available insulins. Therefore, hypermotilinemia observed in diabetics except those with nephropathy is due to hypersecretion of motilin, though the mechanism involved could not be clarified in this study.

Exogenous administration of motilin caused the increase of LESP in man (Rosch et al. 1976) and in dogs (Jennewein et al. 1976). On the contrary, endogenous motilin was not correlated with LESP (Hellemans et al. 1976). We also found no correlation between plasma motilin concentrations and the resting LESP or the response of LESP to tetragastrin. These observations suggest that endogenous motilin is little involved in the regulation of LESP, and that the disturbance of LESP in diabetics with diarrhea or diabetics with autonomic neuropathy (others) cannot be explained by motilin.

Gastric emptying, expressed by the concentration of acetaminophen at 45 min after the ingestion, was closely correlated with FMMC, or FIMC in normal subjects, diabetics without complications and diabetics with diarrhea. Since the exogenous administration of motilin at the physiologic concentration causes the significantly accelerated gastric emptying (Christofides et al. 1979, 1981), a significant positive correlation between gastric emptying and FMMC, or FIMC suggests that endogenous motilin also enhances gastric emptying. The significantly accelerated gastric emptying observed in diabetics without complications and diabetics with diarrhea could be due to the significantly high concentrations of plasma motilin. On the other hand, gastric emptying in diabetics with gastroparesis was markedly delayed in spite of hypermotilinemia. It is known that

exogenous administration of motilin causes the interdigestive migrating motor complex (Itoh et al. 1977), and that the elevation of plasma motilin concentration and the occurrence of the interdigestive migrating motor complex are present at the same time in man (Peeters et al. 1980) and in dogs (Itoh et al. 1978). Furthermore, diabetics with gastroparesis have been found to show the lack of the occurrence of the interdigestive migrating motor complex (Malagelada et al. 1980; Fox and Behar 1980). Therefore, the poor contractile activity of smooth muscle of the stomach in response to endogenous motilin is, at least in part, responsible for the delayed gastric emptying in diabetics with gastroparesis.

Some of gut hormones are inactivated mainly by the kidney (Davidson et al. 1973; Curits et al. 1976). In the patients with chronic renal failure, a high level of gut hormones in the plasma is due to the disturbance of renal inactivation and a greater part of gut hormones in the plasma is considered to have little physiologic action. Therefore, the greater part of plasma motilin has little physiologic action of accelerating the gastric emptying in diabetics with nephropathy, resulting in the normal gastric emptying. The mechanism involved in the slightly delayed gastric emptying in spite of hypermotilinema is unclear in diabetics with autonomic neuropathy (others). A slightly low response of smooth muscle of the stomach to endogenous motilin, which is not present as gastroparesis clinically, may be responsible for this slightly delayed gastric emptying.

Ruppin et al. (1976) reported that the exogenous administration of motilin resulted in the acceleration of small bowel transit. We could not find, however, any relationship between endogenous motilin concentrations and small bowel transit time. Therefore, endogenous motilin is considered to be little involved in the regulation of small bowel transit. Furthermore, the normal small bowel transit time in spite of the significant hypermotilinemia in dibetics without complications also suggests the little participation of endogenous motilin in the regulation of small bowel transit.

Diabetics with diarrhea have shown the significantly short small bowel transit time. Corbett et al. (1981) reported the significantly short small bowel transit time in patients with diarrhea due to the irritable bowel syndrome. These observations suggest that the patients with diarrhea show the short small bowel transit time, regardless of the different causes of diarrhea. Whether the marked hypermotilinemia is one of the causes of diarrhea accompanied by the short small bowel transit time or is caused by the hypersecretion secondary to the accelerated motility of small bowel is not clear in this study. However, as mentioned above, since endogenous motilin is not likely to regulate the small bowel transit, the marked hypermotilinemia may not be responsible for the short transit time. On the contrary, small bowel transit time was significantly delayed in diabetics with autonomic neuropathy (others).

Therefore, diabetics with autonomic neuropathy show the delayed small bowel transit when they have the normal bowel movement, while they show the short small bowel transit when they have diarrhea.

In diabetics with gastroparesis, small bowel transit time was shorter than in normal subjects. Furthermore, there was no correlation between gastric emptying and small bowel transit time in normal subjects. These findings suggest that gastric emptying and small bowel transit are independent of each other.

Consequently, from the observations described above, we may conclude that some aspects of the disturbances of gastrointestinal motility in diabetics could be explained by the relationship between motilin and the contractile activity of smooth muscle of the gastrointestinal tract in response to motilin.

References

1) Bond, J.H. & Levitt, M.D. (1975) Investigation of small bowel transit time in man utilizing pulmonary hydrogen (H_2) measurements. *J. Lab. clin. Med.*, **85**, 546–555.
2) Brown, J.C. (1967) Presence of a gastric motor-stimulating property in duodenal extracts. *Gastroenterology*, **52**, 225–229.
3) Brown, J.C., Cook, M.A. & Dryburgh, J.R. (1972) Motilin, a gastric motor activity-stimulating polypeptide: final purification, amino acid composition, and C-terminal residues. *Gastroenterology*, **62**, 401–404.
4) Christofides, N.D., Modlin, I.M., Fitzpatrick, M.L. & Bloom, S.R. (1979) Effect of motilin on the rate of gastric emptying and gut hormone release during breakfast. *Gastroenterology*, **76**, 903–907.
5) Christofides, N.D., Long, R.G., Fitzpatrick, M.L., McGregor, G.P. & Bloom, S.R. (1981) Effect of motilin on the gastric emptying of glucose and fat in humans. *Gastroenterology*, **80**, 456–460.
6) Corbett, C.L., Thomas, S., Read, N.W., Hobson, N., Bergman, I. & Holdsworth, C.D. (1981) Electrochemical detector for breath hydrogen determination: measurement of small bowel transit time in normal subjects and patients with the irritable bowel syndrome. *Gut*, **22**, 836–840.
7) Curits, P.J., Fender, H.R., Rayford, P.L. & Thompson, J.C. (1976) Catabolism of secretin by the liver and kidney. *Surgery*, **80**, 259–265.
8) Davidson, W.D., Springberg, P.D. & Falkinburg, N.R. (1973) Renal extraction and excretion of endogenous gastrin in the dog. *Gastroenterology*, **64**, 955–961.
9) Dotevall, G. (1961) Gastric emptying in diabetes mellitus. *Acta med. scand.*, **170**, 423–429.
10) Fox, S. & Behar, J. (1980) Pathogenesis of diabetic gastroparesis: a pharmacologic study. *Gastroenterology*, **78**, 757–763.
11) Harasawa, S., Tani, N., Suzuki, S., Miwa, M., Sakita, R., Nomiyama, T. & Miwa, T. (1979) Gastric emptying in normal subjects and patients with peptic ulcer. *Gastroent. Jap.*, **14**, 1–10.
12) Heading, R.C., Nimmo, J., Prescott, L.F. & Tothill, P. (1973) The dependence of paracetamol absorption on the rate of gastric emptying. *Brit. J. Pharmacol.*, **47**, 415–421.
13) Hellemans, J., Vantrappen, G. & Bloom, S.R. (1976) Endogenous motilin and the LES pressure. *Scand. J. Gastroent.*, **11**, Suppl. 39, 67–73.
14) Itoh, Z., Honda, R., Hiwatashi, K., Takeuchi, S., Aizawa, I., Takayanagi, R. & Couch, E.F. (1976) Motilin-induced mechanical activity in the canine alimentary tract. *Scand. J. Gastroent.*, **11**, Suppl. 39, 93–110.
15) Itoh, Z., Takeuchi, S., Aizawa, I. & Takayanagi, R. (1977) Effect of synthetic motilin on gastric motor activity in conscious dogs. *Amer. J. dig. Dis.*, **22**, 813–819.
16) Itoh, Z., Takeuchi, S., Aizawa, I., Mori, K., Taminato, T., Seino, Y., Imura, H. & Yanaihara, N. (1978) Changes in plasma motilin concetration and gastrointestinal contractile activity in conscious dogs. *Amer. J. dig. Dis.*, **23**, 929–935.
17) Jennewein, H.M., Bayer R., Hummelt, H., Lepsin, G., Siewert, R. & Waldeck, F. (1976)

Motilin effects on gastrointestinal motility and lower esophageal sphincter (LES) pressure in dogs. *Scand. J. Gastroent.*, **11**, Suppl. 39, 63–65.

18) Malagelada, J.R., Rees, W.W., Mazzotta, L.J. & Go, V.L.W. (1980) Gastric motor abnormalities in diabetic and postvagotomy gastroparesis: effect of metoclopramide and bethanecol. *Gastroenterology*, **78**, 286–293.

19) Mandelstram, P., Siegel, C.I., Lieber, A. & Siegel, M. (1969) The swallowing disorder in patients with diabetic neuropathy-gastroenteropathy. *Gastroenterology*, **56**, 1–12.

20) Maruhama, Y., Nagasaki, A., Kanazawa, Y., Hirakawa, H., Goto, Y., Nishiyama, H., Kishimoto, Y. & Shimoyama, T. (1980) Effect of a glucoside-hydrolase inhibitor (Bay g 5421) on serum lipids, lipoproteins and bile acids, fecal fat and bacterial flora, and intestinal gas production in hyperlipidemic patients. *Tohoku J. exp. Med.*, **132**, 453–462.

21) Metz, G., Gassull, M.A., Leeds, A.R., Blendis, L.M. & Jenkins, D.J.A. (1976) A simple method of measuring breath hydrogen in carbohydrate malabsorption by end-expiratory sampling. *Clin. Sci. mol. Med.*, **50**, 237–240.

22) Nagasaki, A., Ishimori, A., Masamune, .O. & Yamagata, S. (1977) Rosponse of lower esophageal sphincter pressure to beef soup or AOC-tetrapeptide stimulation in esophagitis. *Tohoku J. exp. Med.*, **121**, 91–97.

23) Peeters, T.L., Vantrappen, G. & Janssens, J. (1980) Fasting plasma motilin levels are related to the interdigestive motility complex. *Gastroenterology*, **79**, 716–719.

24) Rosch, W., Lux, G., Domschke, S., Domschke, W., Wunsch, E., Jaegu, E. & Demling, L. (1976) Effect of 13-nle-motilin on lower esophageal sphincter pressure (LESP) in man. *Gastroenterology*, **70**, 931.

25) Routh, J.I., Shane, N.A., Arredondo, E.G. & Paul, W.D. (1968) Determination of N-acetyl-p-aminophenol in plasma. *Clin. Chem.*, **14**, 882–889.

26) Ruppin, H., Sturm, G., Westhoff, D., Domschke, S., Domschke, W., Wunsch, E. & Demling, L. (1976) Effect of 13-nle-motilin on small intestinal transit time in healthy subjects. *Scand. J. Gastroent.*, **11**, Suppl. 39, 85–88.

27) Scarpello J.H.B., Greaves, M. & Sladen, G.E. (1976) Small intestinal transit in diabetics. *Brit. med. J.*, **2**, 1225–1226.

28) Shima, K., Tanaka, A., Sawazaki, N., Hamabe, J., Tanaka, R., Kumahara, Y. & Yanaihara, N. (1979) Hypermotilinemia in chronic renal failure. *Horm. Metab. Res.*, **11**, 320–321.

29) Shin, S., Hashimura, E., Imagawa, K., Shimizu, F., Yanaihara, C. & Yanaihara, N. (1980) Heterogeneity of immunoreactive motilin. *Endocr. Jap.*, **27**, Suppl. S.R. No. 1, 141–143.