Review

Pathophysiology and Treatment of Diabetic Diarrhea

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Introduction

Diabetic diarrhea was first reported by Bargen et al. in 19361, and was recognized as one symptom of diabetic neuropathy by Rundles in 19452. While the frequency of diabetic diarrhea is reported as 8 to 22%3, only a small number of clinical etiological studies have been reported, and the real frequency is unknown. Our experience of twenty years revealed that 40 of 4,000 diabetics were diagnosed as diabetic diarrhea, showing a frequency of 1.0%.

On the other hand, while no definite causes of diabetic diarrhea are known yet, various possibilities have been presented, e.g., anorectal dysfunction (anal sphincter disorder)3-6, abnormal small bowel transit time7-10, abnormal small bowel secretion7,11, bacterial overgrowth in the small intestine10,12,13, malabsorption of bile acids14,15, concomitant celiac sprue17, abnormalities in regulation of gastrointestinal hormone secretion (motilin)16, an increase in hydroxy fatty acids15 and short chain carboxylic acids17. Other possible causes (or results) of diabetic diarrhea, such as abnormal intracolonic pressure, have been also reported.

1. Definition of diabetic diarrhea

Bargen et al. reported in 19361 unexplainable concomitant diarrhea in severe diabetic patients. Subsequently, diarrhea of diabetic patients with generalized neuropathy (autonomic neuropathy) in whom the blood sugar level remained unstable and other definite causes of diarrhea could be excluded are called diabetic diarrhea. In particular, long duration of diabetes and coexistence of autonomic neuropathy (e.g., postural hypotension, abnormal sweating, impotence or hyphedonia, retrograde ejaculation, atonic bladder, and symptoms suggesting gastroparesis such as abdominal distention at fasting, nausea and vomiting in the early morning) are likely in diabetics with diabetic diarrhea. In diabetic diarrhea, brown, watery, bulky stool are often found and undigested food and/or tenesmus are observed in some cases. Defecation occurs more frequently at night than in the daytime, and incontinencia faecalis may be present concomitantly. Intermittent normal feces or alternate constipation and diarrhea may be observed. In general, abdominal pain does not occur. Other possible causes of diarrhea, e.g., other organic diseases, irritable bowel syndrome, and administration (or abuse) of laxatives, must be excluded in the diagnosis of diabetic diarrhea.

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2. Mechanism of diabetic diarrhea

As shown in Table 1, movement of the small intestine is ingeniously regulated by multiple factors, e.g., electrical characteristics of the smooth muscle of the small intestine, intrinsic and extrinsic nerve tracts (sympathetic and parasympathetic nerves), peptidergic transmitters and balance of gastrointestinal hormones. The extrinsic nerve modulates intrinsic nerve reaction and integrates intrinsic nerve activities\(^3\). If the extrinsic nerve is damaged, therefore, gastrointestinal motility is impaired to a great extent. In other words, when the autonomic nerve tract is sectioned or impaired by, e.g., vagotomy, sympathectomy, ganglion blockers, amyloidosis or primary visceral neuropathy, intractable diarrhea occurs. In diabetics, histological evidence of autonomic nerve impairment is observed; the density of the unmyelinated axon and the diameter of the vagal axon decrease. In the sympathetic nerve, giant neurons and/or dendrite swelling of the postganglionic neuron may be present, and the fiber density of the splanchnic nerve decreases\(^22\). It is reported in patients with diabetic diarrhea that the Auerbach plexus alters greatly\(^23\) and atrophy of the plexus due to angiopathy in the small bowel mucosa is observed\(^24\). In contrast, some investigators report that there are no differences between diabetics with diabetic diarrhea and control subjects in findings such as ganglionic cells of the autonomic nerve and chromatolysis, pyknosis and vacuolization of the small bowel mucosa, and no alteration is found in either of the mucosa, muscularis or vasculature\(^25\).

In streptozotocin-induced diabetic rats, the sympathetic nerves decrease in the plexus myentericus, and fasting and postprandial impairment of the small bowel motility develops. At fasting, the rate of spreading of interdigestive migrating motor complex (MMC) becomes abnormal\(^26\).

In patients with diabetic diarrhea, disorders of the smooth muscle are present in addition to neuropathy; tone of the upper small intestine decreases and peristaltic activity (the frequency and amplitude of the large wave) increases\(^19\). Integrating these nervous system factors and disorders of small bowel smooth muscle function, therefore, it can be said also at the level

| Table 1. Mechanisms of diabetic diarrhea |
|------------------------------------------|
| 1. Autonomic neuropathy: histological changes, angiopathy, migrating motor complex abnormality. |
| 2. Smooth muscle disorders: tone and peristaltic activity |
| 3. Changes of products in alimentary canal: bacterial overgrowth, increases of free bile acids, hydroxy stearic acids and short-chain fatty acids (carboxylic acids) |
| 4. Abnormal small bowel transit time and secretion |
| 5. complicated by celiac sprue and bile acid malabsorption |
| 6. changes of gastrointestinal hormones |
| 7. changes of intracolonic pressure |
| 8. Anorectal dysfunction |
| 9. others: lactose intolerance, α-glucosidase inhibitor, sorbitol malabsorption, abuse of laxatives |
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of the small intestine that diabetic diarrhea is a heterogenous syndrome\textsuperscript{20}. In other words, small bowel transit time may be increased\textsuperscript{27} or decreased\textsuperscript{9}, even if suspected patients are diagnosed as diabetic diarrhea. When the transit time is increased, it is easy to predict that diarrhea generally occurs. When it is decreased\textsuperscript{9}, however, ileocecal bacterial flora in the large bowel ascend into the small intestine, bacterial overgrowth preceeds, and large amounts of cathartic products are produced, resulting in diarrhea.

To overcome these problems, it is required to develop a method to make frequent and repeated detection of transit time from the stomach to the large intestine without severe stress to the patient as possible. For example, it is important to measure and assess the entire gastrointestinal transit time by using markers at different stages where different pathophysiological conditions, e.g., diarrhea or constipation, appear\textsuperscript{28}.

In patients with systemic sclerosis, MMC disappears, small bowel motility decreases, and bacterial overgrowth is observed. Bile acids, which are essential for digestion and absorption of fats in the small intestine, play their roles by forming micelles. It is conjugated bile acids that are required for micelle formation. In the presence of bacterial overgrowth, conjugated bile acids become free bile acids by bacterial deconjugation enzymes, resulting in micelle malformation. Steatorrhea occurs subsequently as a result of this abnormality.

Bacterial overgrowth in patients with diabetic diarrhea is evident because it is reported that bacteria are found in the upper gastrointestinal tract (in the stomach)\textsuperscript{29,30} as well as in the small intestine\textsuperscript{31,32}, where \textbf{10}^6/ml or more of bacteria are detected. In contrast, from the results of our examination of fecal bacterial count in patients with diabetic diarrhea, there were no differences when compared with a control group with respect to obligatory anaerobe count. A significant increase was observed, however in facultative anaerobe count in the diarrreal patients (7.40 vs. 8.47 [log N/g]\textsuperscript{12}). These results are similar to those of an investigation in patients with bacterial overgrowth syndrome due to other factors.

In addition to measurement of intestinal bacteria count, respiratory gas analysis and fecal analysis are well known as measures to make definite diagnosis of bacterial overgrowth syndrome. In the former method, \textit{14}C-cholylglycine is given orally and expiratory \textit{14}CO\textsubscript{2} is analyzed. The expiratory \textit{14}CO\textsubscript{2} level significantly increases in some cases of diabetic diarrhea, meaning that conjugated bile acids are deconjugated by excessively proliferated bacteria in the small intestine\textsuperscript{33,34}. Furthermore, similar results were obtained in a study measuring the level of hydroxy fatty acids in feces\textsuperscript{15}. Hydroxy fatty acids are similar in both structure and pharmacological action to the main component of castor oil (Ricinus\textsubscript{oil}, recinoleic acid)\textsuperscript{36}. In humans, dietary neutral fats are hydrolyzed and hydroxyl reaction occurring at the double bond in the 10th position of resultant oleic acid leads to the formation of an hydroxy fatty acid\textsuperscript{37}. This hydroxylic fatty acid is equivalent to castor oil (12-OH-\(\Delta^9,10\)-octadecanoic acid). Since hydroxy fatty acids are generated by intestinal bacteria, measurement of the level of the acids means indirect monitoring of bacterial overgrowth in the small intestine. When hydroxy fatty acids move through the large intestine, water and electrolytes may be secreted from the large bowel mucosa, leading to diarrhea\textsuperscript{38}. Accordingly, since pancreatic lipase acitivity decreases in pancreatic maldigestion and malabsorption and hydrolysis of dietary neutral fats is impaired, formation of oleic acid, is insufficient and lesser amounts of hydroxylic fatty acids are
generated$^{39,40,41}$. In patients with diabetic diarrhea, the percentage of hydroxy fatty acids to total fatty acids in feces is 10% or more (around 2% in healthy people), showing obvious acceleration of hydroxyl reaction$^{15}$.

Since steatorrhea is not observed in Japanese patients with diabetic diarrhea, total amounts of hydroxy fatty acids excreted in feces are not excessive. In a European study, diabetic diarrhea was complicated by steatorrhea in 9 (33%) of 27 cases, and the total amount of fecal fat excretion reached 20 g or more in three patients$^{4}$. It is impossible, therefore, to exclude the possibility that pathophysiology of diabetic diarrhea may be different between European/American and Japanese patients in relation to substantial differences in the daily consumption of diet, particularly dietary fat consumption (Europeans/Americans: \( \geq 100 \text{ g/day} \); Japanese: 35~40 g/day$^{13}$).

Bile acids are synthesized in the liver and stored in the gallbladder. It is excreted into the small intestine and most of the excreted bile acids are resorbed from the ileum after micelle formation at digestion and absorption of fats. When ileal resorption of bile acids is impaired, large amounts of bile acids flow into the large intestine. Ileal disorders typically appear in Crohn’s disease and after ileal resection in patients with ileal tuberculosis, and are called bile acid malabsorption syndromes$^{42,43}$. Similar to the case of chenodeoxycholic acid administration to dissolve gallstones or of cholera (cholera toxin), large amounts of bile acids flowing into the large bowel activate cyclic AMP in the mucosa of the large intestine, inhibit resorption of water and electrolytes, and induce diarrhea$^{44}$. However, the amount of fecal bile acid excretion in diabetic diarrheal patients is approximately three times that of healthy subjects$^{14,15}$, and this is far less than that of diarrheal patients after ileal resection or vagotomy, in whom the amount of bile acids excreted in feces is eight to ten times that of healthy subjects$^{45-47}$. Therefore, although malabsorption of bile acids is, one pathophysiological condition of diabetic diarrhea$^{14,15}$, it cannot be asserted that bile acid malabsorption induces diarrhea.

When bacterial overgrowth occurs in the small intestine, intestinal bacteria can deconjugate conjugated bile acids to free bile acids and induce micelle malformation$^{32,48}$. Next, we will examine fermentation products in the gastro-intestinal tract, particularly short-chain carboxylic acids. Short-chain carboxylic acids consist of volatile acetic acid, propionic acid, n-butyric acid, isobutyric acid, n-valeric acid, isovaleric acid, unvolatile lactic acid and succinic acid. These short-chain carboxylic acids are physiologically produced from e.g., undigested carbohydrates and dietary fibers by bacteria in the large intestine, and are associated with softening of feces and dilution of toxic substances. Fecal short-chain carboxylic acids increase vastly in pathological conditions, e.g., lactose intolerance based on indigestion of lactose contained in milk in the small bowel membrane$^{49}$, or indigestion and malabsorption of carbohydrates and protein due to pancreatic dysfunction such as chronic pancreatitis$^{50}$. Similarly, \( \alpha \)-glucosidase inhibitors, which are used to inhibit or delay a post-prandial increase in blood glucose level in diabetics, inhibit degradation of starch and disaccharides, and undigested carbohydrates are subject to fermentation reaction by bacteria, resulting in formation of short chain carboxylic acids in large amounts$^{51}$.

Fermentation reaction of carbohydrates in the small intestine is promoted in patients with
diabetic diarrhea, and the amount of formation of short-chain carboxylic acids is approximately three times that of healthy subjects\(^\text{17}\). While the large amounts of short-chain carboxylic acids are partially reabsorbed from the large bowel mucosa\(^\text{52}\), it is considered that unreabsorbed parts may induce osmotic diarrhea.

Retrograde colonography shows images of hypotonic distended large bowel in diabetic diarrhea patients. Residues may sometimes be observed in the large intestine in spite of diarrhea. As clinical physical findings, abdominal tympanitic notes and, in many cases, gargling sounds are noted. Many cases of abdominal simple x-ray pictures show diffuse residues in the large intestine as well as intragastric dietary residues. Based on these findings, it is easy to predict that the large bowel motility is depressed. Battle et al. reported\(^\text{53,54}\) that myoelectrical motor abnormality of the large bowel and disappearance of gastrocolic response after a meal in diabetic diarrheal patients. In contrast, an increase in motor activity is observed in measurement of intrasigmoidal pressure of patients with diabetic diarrhea\(^\text{55}\).

In our cooperative study with Sasaki et al., intracolonic pressure was measured in diabetic diarrheal patients, and changes in intracolonlic pressure and defecograms were examined. A total of 11 subjects whom we diagnosed as diabetic diarrhea based on clinical symptomatology were included in the study. Two of three patients who were reevaluated by detailed history taking and review of any history of chronic drug administration were diagnosed as irritable bowel syndrome. One other subject was diagnosed as chronic diarrhea due to long-term administration of laxatives.

Except for one patient who has currently normal bowel movements (previously considered as a typical case of diabetic diarrhea), some changes were noted in intracolonic pressure. In other words, except for one patient, abnormal findings were observed in intracolonic pressure measurements in seven of eight diabetic diarrheal patients. Various intracolonic pressure curves were obtained; lead tube-like disappearance of segments along the entire intestinal tract was found in two patients, hypotonic spastic constipation from the ascending to descending colon in two, atonic and disappearance of segmental movement in one patient, atonic and spastic coordination in one and spasm limited to the right side of the colon in one. From measurements of intracolonic pressure, excessive reaction to neostigmine was noted in two patients. Defecograms were normal in all subjects. Accordingly, although similar diarrheal symptoms were observed in these subjects, various findings were found with respect to intracolonic pressure measurement. Abnormalities were limited to the right side of the colon in some patients while abnormalities spread to the entire large intestine in other subjects. Furthermore, excessive reaction to neostigmine occurred in two patients, and other various findings, e.g., atonic or spastic coordination, were observed. This diversity provides obstacles in the selection of treatment of diabetic diarrhea.

Among the 40 diabetic diarrheal patients we have experienced, fecal incontinence was observed in four patients (10\%). In a report of Schiller et al.\(^\text{4}\), concomitant fecal incontinence occurs in 20\% of patients with diabetic diarrhea. In these patients, the amount of fecal discharge is not large, and it is estimated that this type of incontinence results from impairment of the anorectal sensory system and reflex mechanism\(^\text{5}\). Results of rectal biopsy in patients with diabetic enteropathy showed denaturation of the plexus submucosus (Meissner), swelling
of axons and, in half of patients, thickening of the basement membrane of the Schwann’s cell and an increase in lysosome, lipofuscin and/or glycogen. Disorders of the sympathetic nerves of the musculus sphincter internus and impairment of the smooth muscle itself are also assumed. It is not considered, therefore that motor function disorders are involved in fecal incontinence in diabetic diarrhea patients.

When chronic pancreatitis is complicated by pancreatic dysfunction, steatorrhea occurs. In contrast, in patients with insulin-dependent diabetes mellitus (IDDM), in whom insulin is completely lacking, enzyme secretion capacity of the pancreas decreases, and this pathological condition is called diabetic pancreatic disorder. Insulin secreted from the β cell of the Langerhans’ islets in the pancreas flows into the portal vein after perfusing the acinar cell. This is called the insulino–acinar axis, and is considered to regulate the protein synthesis of the acinar cell. In fact, insulin promotes expression of the mRNA gene of the acinar cell. In clinical pancreozymin–secretin test (secretin test) in IDDM patients, although not to the extent as in the case of chronic pancreatitis, pancreatic amylase secretion is specifically impaired. Insulin therapy improves the amylase secretion from the pancreas in this pathological condition. While some investigators think that these impairments of pancreatic enzyme secretion induce diabetic diarrhea, they are not severe enough to result in impairment of digestion and absorption of diets. It is also reported that pancreatic exocrine function is normal in diabetic diarrheal patients. Furthermore, although it is reported that pancreatic exocrine function is also inhibited by morphological changes such as atrophy of the pancreas, a decrease in cholinergic enteropancreatic reflex, and hyperglucagonemia, their relationship with diabetic diarrhea is unclear.

Hypersecretion of small intestine fluids is also one of the pathophysiological conditions of diarrhea. Severe watery stool is observed in patients with a vasoactive intestinal polypeptide (VIP)-producing tumor. In contrast, persistent constipation occurs in patients with the adrenaline-producing tumor (pheochromocytoma). Since autonomic neuropathy is present in diabetic diarrhea, adrenergic regulation decreases, resorption capacity of water and electrolytes in the small intestine is reduced, possibly resulting in diarrhea. There is a report showing that the α2-adrenergic agonist clonidine hydrochloride is extremely effective against diabetic diarrhea. There is also a report showing that long-acting somatostatin derivates, which inhibit hormonal activities at all hormone secretion and receptor levels, are effective against diabetic diarrhea.

From the Europe, it is reported that some cases of diabetic diarrhea may be complicated by celiac sprue. Since celiac sprue disappears with gluten free diet, its relationship with diabetic diarrhea is examined. In Japan, however, there is no case report of diabetic diarrhea complicated by celiac sprue. It is advisable to understand, therefore, that there is no association between diabetic diarrhea and celiac sprue in Japan.

In view of other factors, diabetic diarrhea is also examined with respect to diet. For example, it is reported that sorbitol, which is contained as a sweetener in (saccharose-free) soft drinks and chewing gums, increases intestinal osmotic pressure, and 10 g sorbitol induces diarrhea even in healthy subjects, i.e., sorbitol induced diarrhea. Lactose intolerance, frequently seen in Japanese, must also be differentiated from diabetic diarrhea. Furthermore,
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attention should also be paid to administration of \( \alpha \)-glucosidase inhibitors, which are inhibitors of post-prandial blood glucose elevation currently on the market\(^{51}\), and chronic laxative treatment for constipation.

3. Diseases which should be differentiated

Diabetic patients are to be diagnosed as diabetic diarrhea if diabetes is complicated by peripheral autonomic neuropathy, the clinical picture mentioned in the section of definition of diabetic diarrhea is observed, and other diseases which may be possible causes of diarrhea are excluded. Even when these symptoms are noted, however, other types of diarrhea may occur in some diseases.

As mentioned previously, two of our 11 patients diagnosed as diabetic diarrhea were subsequently diagnosed as irritable bowel syndrome based on measurements of intracolonic pressure and detailed review of medical history.

We also experienced diabetic patients with concomitant diabetic autonomic neuropathy who became lambliasis and pancreatic steatorrhea secondary to chronic pancreatitis in the course of diabetes and were difficult to differentiate from diabetic diarrhea. The following are case reports of these patients.

51-year-old male patient. He was diagnosed as diabetes mellitus at the age of 46. He noticed dysesthesia in the lower extremities and impotence around age 51. He worked in Kanagawa as a seasonal worker since 40 for five years, during which he used to drink unboiled tap water frequently. Since age 51, he experienced repeated painless watery diarrhea and, sometimes, vomiting and postural hypotension in the early morning. Since diabetic diarrhea

Fig. 1. Many Giardia lamblia are seen in the duodenal fluid.
or pancreatic diarrhea (due to pancreatic cancer or chronic pancreatitis) was suspected, pancreozymin-secretin test was performed. For cytodiagnosis, duodenal fluid was examined under microscopy, and many *Giardia lamblia* were seen as shown in Fig. 1. Small intestine biopsy showed many *Giardia lamblia* adhering to the intestinal mucosa (Fig. 2, scanning electron microscopic image). Small intestine biopsy was performed once again after 7 days of Frasyl administration, showing no evidence of *Giardia lamblia*. Currently, for more than 10 years, relapse of *lamblia* infection has not been confirmed. Accordingly, *Giardia lamblia* infection should be differentiated from diabetic diarrhea.

Next case was a patient with chronic pancreatitis during decompensated stage, and his condition was complicated by steatorrhea and autonomic neuropathy due to pancreatic diabetes. Because of the latter disorder, diabetes was complicated by steatorrhea.

52-year-old male patient. He used to drink Japanese sake at a daily average of 1.8 L since 16 years of age. He experienced an attack of pancreatitis (pancreatic pain) at age 34. At age 40, he became overt diabetes and started insulin treatment. At age 45, he was diagnosed as pancreatolithiasis based on abdominal simple x-ray images and ERCP. Since age 42, he suffers from dysesthesia in the lower extremities and subsequent postural hypotension and impotence. Since age 43, steatorrhea was observed. Furthermore, watery steatorrhea continued for around five days sometimes. When he showed diabetic diarrheal symptoms, 23.4 g of fats were excreted in feces after 30 g of fat intake, and 13.8% of fecal fatty acids were hydroxy fatty acids. After antibiotic treatment, the percentage of hydroxy fatty acids in feces returned to the normal level of 1.2%, although fecal fat excretion remained unchanged, i.e., 25.0 g. Diarrhea also disappeared and, the feces became typical for pancreatic steatorrhea, thick, pale yellow and formed. As in this patient, pancreatic steatorrhea may be complicated by
diabetic diarrhea, and attention should be directed to the differential diagnosis of diabetic diarrhea.

Other diseases and conditions which should be differentiated include irritable bowel syndrome (previously mentioned), inflammatory bowel diseases, celiac sprue, infectious enterocolitis, lactose intolerance, sorbitol intake, and so on.

4. Treatment of diabetic diarrhea

As a general treatment of diabetic diarrhea, fluid replacement may be required for the treatment of dehydration and to revise electrolyte balance when diarrhea persists.

In the case of dietary control of diabetic diarrhea, milk and sorbitol as sweeteners should be avoided and bowel movements should be regular not to induce constipation. When constipation occurs, bacterial overgrowth may progress.

As shown in Table 2, injection of elementary diet (ED) into the jejunum is reported\(^75\). This ED therapy is based on a concept similar to that of treatment of, e.g., Chohn's disease\(^76\). It is considered that the ED therapy improves bacterial overgrowth, inhibits pancreatic exocrine function and decreases enteric residues to make the small intestine rest\(^77\). It is considered, therefore, that rest of the intestinal tract is important in the treatment of diabetic diarrhea.

In the above-mentioned case of pancreatic steatorrhea complicated by diabetic diarrhea, replacement of large amounts of pancreatic digestive enzyme\(^78,79\) and, in some cases, concomitant acid secretion inhibitors (e.g., cimetidine, proton pump inhibitors)\(^80,81\) may be required.

The narcotic antidiarrheal agent loperamide is used as the first-choice treatment of diabetic diarrhea. Loperamide binds to the opiate receptor, which is localized to the cholinergic and non-adrenergic nerves, decreases release of acetylcholine and prostaglandins, both of which dilate the intestinal tract in the annular direction, and inhibits intestinal peristalsis\(^82,83\). While its pharmacological action is similar to that of morphine, Loperamide is considered to have no effects on the central nervous system as it does not pass the blood brain barrier\(^84\). Broad spectrum antibiotics are also used as the first-choice agent for diabetic diarrhea. Initially, tetracycline\(^85\) and macrolides\(^86,87\), both of which were said to be effective against 70% of diabetic diarrheal patients, were used, while amoxillin • potassium clavulanate (Augmentin)

| 1. | Elemental diet (ED) |
| 2. | Pancreatic extracts |
| 3. | Antidiarrheal agents: Loperamide |
| 4. | Broad spectrum antibiotics |
| 5. | Macrolides: antibacterial action and motilide mechanism |
| 6. | Anion exchange resin: cholestyramine |
| 7. | \(\alpha\)-receptor agonist |
| 8. | Long-acting somatostatin: Octreotide acetate |
| 9. | Gastrokinetics and anticholinergics: Aclatoniun napadisilate, Trimebutine maleate, Tiquizium bromide, Cispide |
is currently used. Since 10⁵/g of *Clostridium difficile* were detected in bacteriological examination of feces of our diabetic diarrheal patients and D1–toxin positive patients are reported\(^{12}\), metronidazole may also be effective. However, there are definite differences in pathophysiological conditions between pseudomembraneous colitis, where *Clostridium difficile* is pure cultured, and diabetic diarrhea.

Cephalosporin, new quinolones and chloramphenicol\(^{88}\) may be effective in some cases of diabetic diarrhea. Effectiveness of these antibiotics against diabetic diarrhea is an indirect evidence that bacterial overgrowth is one pathophysiological condition of diabetic diarrhea. Specifically, three days of antibiotic treatment is adequate to improve bacterial overgrowth, and aimless long-term therapy should be avoided.

It has become apparent recently that macrolides act as motilide on gastrointestinal motility\(^{89}\). When the effect of macrolides on diabetic diarrhea is evaluated, therefore, it is required to investigate in view of not only antibacterial action on enteric bacteria but also promotive effects on gastrointestinal motility. In fact, we confirmed that intravenous drip infusion of EM523L provides immediate improvement of diabetic diarrhea as well as of gastric motility disorder in diabetic diarrheal patients with concomitant diabetic gastroparesis.

It should also be taken into consideration that bile acid malabsorption exists in severe, intractable diabetic diarrhea\(^{14,15}\). Among bile acids, deoxycholic acid or chenodeoxycholic acid increases cyclic AMP activity in the large bowel mucosa and inhibits absorption of water and electrolytes from the mucosa\(^{90}\). An anion exchange resin (cholestyramine) is required, therefore, to adsorb large amounts of dihydroxy bile acids and to inhibit effects of bile acids on cyclic AMP. Cholestyramine is reportedly useful against post–vagotomy intractable diarrhea\(^{91,92}\) and diabetic diarrhea\(^{91}\). Cholestyramine is also extremely effective against diarrhea after ileal resection, where resorption sites of bile acids are depleted\(^{93}\). Difficulty in ingestion and induction of steatorrhea in some cases\(^{94}\) are drawbacks of cholestyramine.

In contrast, the ß₂-receptor agonist clonidine hydrochloride, a stimulant of sympathetic nerve function, may delay small bowel transit time\(^{67}\) and inhibit diarrhea\(^{11,67}\) in patients with diabetic diarrhea.

The long-acting somatostatin (octreotide acetate) provides effects similar to those of systemic administration of the paracrine somatostatin. It is considered that octreotide acetate inhibits diarrhea by inhibiting enteric secretion of water and electrolytes\(^{58}\). Furthermore, it is useful for the treatment of pancreatic cholera\(^{95}\) or ileostomy diarrhea\(^{96}\).

Somatostatin inhibits secretion of various hormones. For example, since it inhibits pancreatic exocrine function and bile secretory function significantly, and steatorrhea may be induced\(^{97}\), it should be used with careful monitoring of patients.

It is known that prednisolone is extremely effective against diabetic diarrhea\(^{98}\), but the mechanism is not known.

In view of colonic motor function, single or concomitant administration of agents, e.g., aclatonium napadisilate (Abovis\(^{8}\)), Trimebutine maleate (Cerekinon\(^{8}\)), tiquizium bromide (Thiaton\(^{8}\)) and cisapride (Risamol\(^{8}\)) improve diabetic diarrhea and normalize bowel movements to some extent. It is a fact, however, that the usual dose, three to six capsules (tablets) daily, is not effective to treat the diarrhea; nine to 12 capsules (tablets) daily are used in many cases.
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Trimebutine maleate is similar to procain in chemical structure and to enkephalin in pharmacological action. At low concentrations, since it inhibits noradrenalin synthesis by way of the μ-opioid receptor and acetylcholine relatively becomes predominant, intestinal motility increases. This action is antagonized by naloxane. In contrast, at high concentrations, trimebutine maleate inhibits acetylcholine secretion by way of the μ- and κ-opioid receptors and suppresses intestinal motility. Trimebutine maleate has, therefore, dual regulatory mechanisms on intestinal motility. Trimebutine maleate is useful for patients with spastic ascending colon showing substantial mass movement confirmed in colonic pressure measurement or with concomitant irritable bowel syndrome.

Aclatonium napadisilatate, which is a physiologically active substance contained in puerariae, promotes intestinal motility and prostaglandin F<sub>2α</sub> secretion, and directly stimulates acetylcholine receptors in the Oddi sphincter of the stomach and gallbladder. It is considered useful for patients with underlying diarrhea in whom the entire large intestine is hypotonic and segmental movement decreases.

Tiquizium bromide is a quaternary ammonium chloride having a quinolidine skeleton, and is a peripheral muscarine receptor selective antagonist (M2 antagonist) with parasympatholytic effects. It inhibits the smooth muscle of, e.g., the upper and lower gastrointestinal tract, biliary tract, Oddi sphincter and urinary tract. Compared with atropin sulfate or butylscopolamin bromide, occurrence of photophobia, dry mouth and dysuria are less frequent. Tiquizium bromide is useful in patients with diabetic diarrhea complicated by irritable colon or spastic constipation.

In conclusion, this paper reports on the pathophysiology and treatment of diabetic diarrhea. It is considered from the examination of its pathophysiology that diabetic diarrhea may be induced not by a single cause but by a multiple factors. Diabetic diarrhea is unlikely if no concomitant diabetic neuropathy, particularly autonomic neuropathy, is observed.

References

1) Bargen, J.A., Bollman, J.L. and Keple, E.J. (1936). The “diarrhea of diabetes” and steatorrhea of pancreatic insufficiency. Proc Staff Meet Mayo Clin 11: 737-742.
2) Rundles, R.W. (1945). Diabetic neuropathy: General view with report 125 cases. Medicine (Baltimore) 24: 111-160.
3) Valdovinos, M.A., Camilleri, M. and Zimmerman, B.B. (1993). Chronic diarrhea in diabetics mellitus: Mechanisms and an approach to diagnosis and treatment. Mayo Clin Proc. 68: 691-702.
4) Schiller, L.R., Santa, Ana, C.A., Schumulen, A.C., Hendler, R.S., Harford, W.V. and Fordtran, J.S. (1982). Pathogenesis of fecal incontinence in diabetes mellitus, Evidence for internal-anal sphincter dysfunction. N. Engl. J. Med. 307: 1666-1671.
5) Katz, L.A., Kaufmann, H.J. and Spiro, H.M. (1967). Anal sphincter pressure characteristics. Gastroenterology 52: 513-518.
6) Read, N.W., Harford, W.V., Schumulen, A.C., Read, M.G., Santa, Ana, C.A. and Fordtran, J.S. (1979). A clinical study of patients with fecal incontinence and diarrhea. Gastroenterology 76: 747-756.
7) Vinnik, I.E., Kern, F.Jr. and Struthers, J.E. Jr. (1962). Malabsorption and the diarrhea of
diabetes mellitus. *Gastroenterology* 43: 507-529.

8) Berge, K.G., Sprague, R.G. and Bennett, W.A. (1956). The intestinal tract in diabetic diarrhea. A pathologic study. *Diabetes* 5: 289-294.

9) Hodges, F.J., Rundles, R.W. and Hanelin, J. (1947). Roentgenologic study of the small intestine. II. Dysfunction associated with neurologic diseases. *Radiology* 49: 659-673.

10) Scarpello, J.H.B., Greaves, M. and Sladen, G.E. (1976). Small intestinal transit in diabetics. *Brit. Med. J.* 20: 1225-1226.

11) Fedorak, R.N., Field, M. and Chang, E.B. (1985). Treatment of diabetic diarrhea with clonidine. *Ann. Intern. Med.* 102: 197-199.

12) Nakamura, T., Akai, H., Hongo, M., Imai, N., Toyota, R., Goto, Y., Okuguchi, F. and Komatsu, K. (1983). Disturbances of the patients with diabetes mellitus. *Tohoku J. Exp. Med.* 139: 205-215.

13) Goldstein, F., Wirt, C.W. and Kowlessar, O.D. (1970). Diabetic diarrhea: Microbiologic and clinical observation. *Ann. Intern. Med.* 72: 215-218.

14) Molloy, A.M. and Tomkin, G.H. (1978). Altered bile in diabetic diarrhea. *Brit. Med. J.* II: 1462-1463.

15) Nakamura, T., Imamura, K., Tsushima, F., Kikuchi, H. and Takabe, A. (1993). Fecal excretions of hydroxy fatty acid and bile acid in diabetic diarrheal patients. *J. Diab. Comp.* 7: 8-11.

16) Nakanome, C., Akai, H., Hongo, M., Imai, N., Toyota, R., Goto, Y., Okuguchi, F. and Komatsu, K. (1983). Disturbances of the patinets with diabetes mellitus. *Tohoku J. Exp. Med.* 139: 205-115.

17) Nakanome, C., Akai, H., Hongo, M., Imai, N., Toyota, R., Goto, Y., Okuguchi, F. and Komatsu, K. (1983). Disturbances of the patients with diabetes mellitus. *Tohoku J. Exp. Med.* 139: 205-115.

18) Lux, G. (1989). Gastrointestinale MotilitatsstOungen-Diabetes mellitus. *Leber-Magen-Darm* 19: 84-93.

19) Schrub, J.-CI., Hillemand, B. and Clabaut, Y. (1969). Les troubles de malabsorption et la diarrhée chez le diabétique. *Sem. Hsp. Paris* 45: 3173-3179.

20) Atkinson, M. and Hoskin, D.J. (1983). Gastrointestinal complication of diabetes mellitus. *Clinics in Gastroenterology* 12: 633.

21) Barkin, J.S. and Skyler, J.S. (1983). Diabetes and the gastorintestinal system. Ellenberg M and Rifkin H (eds): *Diabetes Mellitus: Theory and practice*, 863-877, Medical Examination Publishing, New York.

22) Hensley, G.T. and Soergel, K.H. (1968). Neurologic findings in diabetic diarrhea. *Arch Path* 85: 587-597.

23) Francois, R. and Mouringuand, C. (1958). Diarrhée incoercible et fatale chez un jeune diabétique : étude des plexus myentériques. *Sem. Hôp. (Paris)* 34: 1526-1531.

24) Drewes, VM. and Olsen, S. (1965). Histological changes in the small bowel in diabetes mellitus. *Acta Path Microbiol Scand* 63: 478-480.

25) Berge, K.G., Wollaeger, E.E., Scholz, D.A., Rooke, E.D. and Sprague, R.G. (1956). Steatorrhea complicating diabetes mellitus with neuropathy. *Diabetes* 5: 25-31.

26) Moncton, G. and Pehowich, E. (1980). Autonomic neuropathy in the streptozotocin diabetic rat. *J. Canada Sci Neurol* 7: 135-142.

27) Keshavarzian, A. and Iber, F.L. (1986). Intestinal transit in insulin-requiring diabetics. *Am. J. Gastroenterol* 8: 257-260.

28) Kawagishi, T., Nishizawa, Y., Okuno, Y., Sekiya, K. and Morii, H. (1992). Segmantal gut transit in diabetes mellitus: Effect of cisapride. *Diab. Res. Clin. Prac.* 17: 137-144.
29) Nakamura, T., Takebe, K., Terada, A., Kudoh, K., Imamura, K., Machida, K. and Kikuchi, H. (1995). Intragastric fermentation in patients with gastroparesis diabeticorum. *J. Clin. Gastroenterol* **20**: 79–80.
30) Nakamura, T., Takebe, K., Terada, A., Kudoh, K., Miyaotaka, K., Nakahata, H., Fukaya, T., Tsunoda, T., Yamada, N., Ishii, M., Kikuchi, H., Kudoh, K., and Takebe, K. (1992). Желудочно-бактериальная флора у больных диабетическим парезом. *Клиническая Медицина* **50**: 9–10.
31) Whalen, G.E., Soergal, C.H. and Greenan, J.E. (1969). Diabetic diarrhea: A clinical and pathological study. *Gastroenterology* **56**: 1021–1032.
32) Goldstein, F., Wirts, C.W. and Kowlessar, O.D. (1970). Diabetic diarrhea and steatorrhea. *Microbiologic and clinical observations. Ann Intern Med.** **72**: 215–218.
33) Scarpello, J.H.B., Hague, R.V., Cullen, D.R. and Sladen, G.E. (1976). The 14C-glycocholate test in diabetic diarrhoea. *Brit. Med. J.* **2**: 673–675.
34) Joliot-A. Y., Descos, L. and Minaire, Y. (1978). Diarrhee des diabétiques. Rôle de la pollulation microbienne entérique. *La Nouvelle Presse Médicale* **7**: 941.
35) James, A.T. and Webb, J.P.W. (1961). The occurrence of unusual fatty acids in fecal lipids from human beings with normal and abnormal fatty absorption. *Biochem J.* **78**: 333–339.
36) Kelly, D.G., Kerlin, P., Sarr, M.G. and Phillips, S.F. (1981). Ricinoleic acid causes secretion in autotransplanted (extrinsically denervated) canine jejunum. *Dig. Dis. Sci.* **26**: 966–970.
37) Thomas, P.J. (1972). Identification of some enteric bacteria which convert oleic acid to hydroxy stearic acid in *vitro*. *Gastroenterology* **62**: 430–435.
38) Bright-Asare, P. and Binder, H.J. (1973). Stimulation of colonic secretion of water and electrolytes by hydroxy fatty acids. *Gastroenterology* **64**: 81–88.
39) Nakamura, T., Imamura, K., Abe, Y., Miyazawa, T., Takebe, K. and Kikuchi, H. (1980). Mild bile acid malabsorption and normal excretion of fecal hydroxy fatty acids in patients with chronic pancreatitis. *Jpn. J. Gastroenterol* **77**: 1770–1776.
40) Kim, Y.S. and Spritz, N. (1968). Hydroxy fatty acid excretion in steatorrhea of pancreatic and nonpancreatic origin. *N. Engl. J. Med.* **279**: 1421–1426.
41) Nakamura, T., Takebe, K., Tando, Y., Arai, Y., Yamada, N., Ishii, M., Kikuchi, H. and Imamura, K. (1995). Faecal triglycerides and fatty acids in the differential diagnosis of pancreatic insufficiency and intestinal malabsorption in patients with low fat intakes. *J. Int. Med. Res.* **23**: 48–55.
42) McLeod, G.M. and Wiggins, H.S. (1968). Bile-salts in small intestinal contents after ileal resection and in other malabsorption syndromes. *Lancet* **1**: 873–876.
43) Hofmann, A.F. and Poley, J.R. (1972). Role of bile acid malabsorption in the pathogenesis of diarrhea and steatorrhea in patients with ileal resection. *Gastroenterology* **62**: 918–934.
44) Mekhjian, H.S., Phillips, S.F. and Hofmann, A.F. (1971). Colonic secretion of water and electrolytes induced by bile acids: perfusion studies in man. *J. Clin. Invest* **50**: 1569.
45) Allan, J.G. and Russel, R.I. (1973). Increased faecal excretion of bile-acids in post-vagotomy diarrhea. *Brit. J. Surg* **60**: 912.
46) Allan, J.G., Gerskowitch, V.P. and Russell, R.I. (1974). The role of bile acids in the pathogenesis of postvagotomy diarrhea. *Brit. J. Surg* **61**: 516–518.
47) Blake, G., Kennedy, T.L. and Mckelvey, S.T.D. (1983). Bile acids and post-vagotomy diarrhea. *Brit. J. Surg* **70**: 177–179.
48) Gorback, S.L. and Tabaqchali, S. (1969). Bacteria, bile and the small bowel. *Gut* **10**: 963–972.
49) Bayless, T.M. and Rosenweig, N.S. (1966). A racial difference in the incidence of lactase deficiency. A survey of milk intolerance and lactase deficiency in healthy adult males. *JAMA* **197**: 968–972.
50) Nakamura, T., Takebe, K., Terada, A., Kudoh, K., Yamada, N., Arai, Y. and Kikuchi, H.
(1993). Short-chain carboxylic acid in the feces in patients with pancreatic insufficiency. *Acta Gastroenterol Belgica* 56: 326–331.

51) Nakamura, T., Takebe, K., Kudo, K., Terada, A., Tando, Y., Arai, Y., Yamada, N., Ishii, M. and Kikuchi, H. (1993). Effect of an α-glucosidase inhibitor (AO-128) on intestinal fermentation and faecal lipids in diabetic patients. *J. Int. Med. Res.* 21: 257–267.

52) Ruppin, H., Bar-Meir, S., Soergel, H., Wood, C.W. and Schmitt, M.G. Jr. (1980). Absorption of short-chain fatty acids by the colon. *Gastroenterology* 78: 1500–1507.

53) Battle, W.M., Cohen, J.D. and Snape, W.J. Jr. (1983). Disorders of colonic motility in patients with diabetes mellitus. *Yale J. Biol. Med.* 56: 277–283.

54) Battle, W.M., Snape, W.J. Jr, Alavi, A., Cohen, S. and Braunstein, S. (1980). Colonic dysfunction in diabetes mellitus. *Gastroenterology* 79: 1217–1221.

55) Kirchmayer, S., Cembala, D. and Cichecka, K. (1968). Kinetyka Jelita grubego w biegunce cukrzycowej. *Przegląd Lekarski* 12: 852–855.

56) Schmidt, H., Riemann, J.F., Schmid, A. and Sailer, D. (1984). Ultrastruktur der diabetischen autonomen Neuropathie des Gastrointestinal-traktes. *Klin Wochenschr* 62: 399–405.

57) Nakamura, T., Takebe, K., Kudoh, K., Ishii, M., Imamura, K., Kikuchi, H., Kasai, F., Tando, Y., Yamada, N., Arai, Y., Terada, A. and Machida, K. (1995). Steatorrhea in Japanese patients with chronic pancreatitis. *J Gastroenterol* 30: 79–83.

58) Imamura, K. (1976). Pancreatic exocrine function in diabetic patient. *Horosaki Med. J.* 28: 532–540.

59) Tsushima, F., Nakamura, T., Kudou, K., Imamura, K. and Takeda, K. (1991). Changes in pancreatic exocrine function in primary diabetes mellitus before and after insulin treatment. *J. Jpn. Pancreas. Soc.* 6: 446–453.

60) Bonner-Weir, S. and Orci, L. (1981). New perspectives on the micro-vasculature of the islets of Langerhans. *Diabetes* 31: 883–889.

61) Korc, M., Owerbach, D., Quinto, C. and Rutter, W.J. (1981). Pancreatic islet–acinar cell interaction: Amylase messenger RNA levels are determined by insulin. *Science* 213: 351–353.

62) Imamura, K., Miyazawa, T., Machida, K., Nakamura, T., Abe, Y., Makino, I. and Takebe, K. (1985). Diabetes mellitus and exocrine pancreatic function. *Biliary tract Pancreas* 6: 291–300.

63) Verner, J. and Morrison, A.B. (1958). Islet cell tumor and a syndrome of refractory watery diarrhea and hypokalemia. *Am. J. Med.* 25: 374–380.

64) Marks, I.N., Bank, S. and Louw, J.H. (1967). Islet cell tumor of the pancreas with reversible watery diarrhea and achlorhydria. *Gastroenterology* 52: 695–708.

65) Short, I.A. and Padfield, P.L. (1976). Malignant phaeochromocytoma with severe constipation and myocardial necrosis. *Br. Med. J.* 2: 793–794.

66) Nakamura, T., Takebe, K., Kudoh, K., Ishii, M., Imamura, K., Kikuchi, H., Kasai, F., Tando, Y., Yamada, N., Arai, Y., Terada, A. and Machida, K. (1994). Decreased counterregulatory hormone responses to insulin-induced hypoglycemia in patients with pancreatic diabetes having autonomic neuropathy. *Tohoku J. Exp. Med.* 174: 305–315.

67) Morali, G.A., Braverman, D.Z., Lissi, J., Goldstein, R. and Jacobsohn, W.Z. (1991). Effect of clonidine on gallbladder contraction and small bowel transit time in insulin-treated diabetics. *Am. J. Gastroenterol* 86: 995–999.

68) Dudl, R.J., Anderson, D.S., Forsythe, A.B., Ziegler, M.G. and O'Dorisio, T.M. (1987). Treatment of diabetic diarrhea and orthostatic hypotension with somatostatin analogue SMS 201-995. *Am. J. Med.* 83: 584–588.

69) Malins, J.M. and Mayne, N. (1969). Diabetic diarrhea: A study of thirteen patients with jejunal biopsy. *Diabetes* 18: 858–866.

70) Von, Noorden, K.H. (1929). Sionon in der Diabetesbehandlung. *Deutsch Med. Wochenschr* 55: 483.
Diabetic diarrhea

71) Gryboski, J.D. (1966). Diarrhea from diabetic candies. *N. Engl. J. Med.* **275**: 718.
72) Ravry, M.J.R. (1980). Dietetic food diarrhea. *JAMA* **244**: 270.
73) Goldberg, L.D. and Ditck, N.T. (1978). Chewing gum diarrhea. *Am. J. Dig. Dis.* **23**: 568.
74) Fritz, Neils, G., Vermeeren, M.A.P., and Jansen, W. (1990). Role of fructose-sorbitol malabsorption in the irritable bowel syndrome. *Gastroenterology* **99**: 1016-1020.
75) Shimizu, H., Shimomura, Y., Takahashi, M., Kobayashi, I., Tomizawa, T. and Kobayashi, T. (1991). Enteral hyperalimentation with continuous subcutaneous insulin infusion improved severe diarrhea in poorly controlled diabetic patient. *J. Parent Enteral Nutr* **15**: 181-183.
76) Greenstein, J.P., Birnbaum, S.M. and Otey, M.C. (1957). Quantitative nutritional studies with water-soluble, chemically defined diet. I. Growth, reproduction and lactation in rats. *Arch Biochem Biophys* **72**: 396-416.
77) Kogoshi, S., Sato, H. and Inoue, G. (1978). On a new product of the elementary diet. *Igaku no Ayumi* **106**: 26-28.
78) Nakamura, T., Takebe, K., Kudoh, K., Ishii, M., Imamura, K., Kikuchi, H., Kasai, F., Tandoh, Y., Yamada, N., Arai, Y., Terada, A. and Machida, K. (1995). Effects of pancreatic digestive enzymes, sodium bicarbonate, and a proton pump inhibitor on steatorrhea caused by pancreatic diseases. *J. Int. Med. Res.* **23**: 37-47.
79) DiMagno, E.P., Malagelada, J.R. Go, V.L.W. and Moertel, C.G. (1977). Fate of orally ingested enzymes in pancreatic insufficiency: Comparison of two dosage schedules. *N. Engl. J. Med.* **296**: 1318-1322.
80) Nakamura, T., Arai, Y., Tandoh, Y., Terada, A., Yamada, N., Tsujino, M., Imamura, K., Machida, K., Kikuchi, H. and Takebe, K. (1995). Effect of omeprazole on changes in gastric and upper small intestine pH levels in patients with chronic pancreatitis. *Clin Therap.* **17**: 448-459.
81) Regan, P.T., Malagelada, J.R., DiMagno, E.P., Glanzman, S.L. and V.L.W. (1977). Comparative effects of antacids, cimetidine and enteric coating on the therapeutic response to oral enzymes in severe pancreatic insufficiency. *N. Engl. J. Med.* **297**: 854-858.
82) Yagasaki, O., Suzuki, H. and Sohji, T. (1978). Effects of loperamide on acetylcholine and prostaglandin release from isolated guinea pig ileum. *Jpn. J. Pharmacol* **28**: 873-882.
83) Muramatsu, M., Fijiwara, M., Sikimi, T. and Nakashima, M. (1979). Effects of loperamide on the guinea pig taenia colli. *Eur. J. Pharmacol* **55**: 181-187.
84) Heel, R.C., Brogden, R.N., Speight, T.M. and Avery, G.S. (1978). Loperamide—a review of its pharmacological properties and therapeutic efficacy in diarrhea. *Drugs* **15**: 33-52.
85) Scarpello, J.H.B., Greaves, M. and Sladen, G.E. (1976). Small intestinal transit in diabetics. *Brit. Med. J.* **2**: 1225-1226.
86) Malins, J.M. and French, J.M. (1957). Diabetic diarrhea. *Q.J. Med.* **26**: 467-480.
87) Green, P.A., Berge, K.G. and Sprague, R.G. (1968). Control of diabetic diarrhea with antibiotic therapy. *Diabetes* **17**: 385-387.
88) Sumi, S.M. and Finlay, J.M. (1961). On the pathogenesis of diabetic steatorrhea. *Ann. Intern. Med.* **55**: 994-997.
89) Nakamura, T., Ishii, M., Arai, Y., Tandoh, Y., Terada, A. and Takebe, K. (1994). Effect of intravenous administration of EM 523L on gastric emptying and blood glucose after a meal in patients with diabetic gastroparesis: A pilot study. *Clin Therap* **16**: 989-999.
90) Corazza, G.R., Ciccarelli, R., Caciagli, F. and Gasbarrini, G. (1979). Cyclic AMP and cyclic GMP levels in human colonic mucosa before and during chenodexoxycholic acid therapy. *Gut* **20**: 498-492.
91) Bousfield, G. and Dick, G. (1973). Cholestyramine and diabetic and post-vagotomy diarrhea. *Br. Med. J.* **17**: 423.
92) Duncombe, V.M., Bolin, TD. and Davis, A.E. (1977). Double-blind trial of cholestyramine in
post-vagotomy diarrhoea. Gut 18: 531–535.

93) Hofmann, A.F. and Poley, J.R. (1969). Cholestyramine treatment of diarrhoea associated with ileal resection. N. Engl. J. Med. 281: 397–402.

94) Nakamura, T., Makino, I., Onuma, T., Tsutsui, M., Osonoi, T., Tamazawa, N., Imamura, K., Takebe, K. and Kikuchi, H. (1984). Effects of dietary fiber on the bowel function of patients with diabetes mellitus. Jap. J. Gastroenterol 81: 1955–1961.

95) Maton, P.N. O'Dorisio, T.M., McArthur, K.E., Howard, J.M., Chermer, J.A., Malarkey, T.B., Collen, M.J., Gardner, J.D., Jensen, R.T. and Howe, B.A. (1985). Effect of a long-acting somatostatin analogue (SMS 201–995) in a patient with pancreatic cholera. N. Engl. J. Med. 312: 17–21.

96) Williams, N.S., Cooper, J.C., Axon, A.T.R., King, R.F.G.J. and Barker, M. (1984). Use of a long-acting somatostatin analogue in controlling life threatening ileostomy diarrhea. Br. Med. J. 289: 1027–1028.

97) Nakamura, T., Kudoh, K., Takebe, K., Imamura, K., Terada, A., Kikuchi, H., Yamada, N., Arai, Y., Tando, Y., Machida, K. and Ishii, M. (1994). Octreotide decreases biliary and pancreatic exocrine function, and induces steatorrhea in healthy subjects. Intern. Med. 33: 539–596.

98) Mailman, R.H. (1958). Steatorrhea with diabetes: a case report. Ann. Intern. Med. 49: 190–192.

99) Nagasaki, M. Kobayashi, T. and Tamaki, H. (1991). Effects of trimebutine on cytosolic Ca2+ and force transitions in intestinal smooth muscle. Eur. J. Pharmacol 195: 317–321.

100) Taniyama, K., Sano, I., Nakayama, S., Matsuyama, S., Takebe, K., Yoshihara, C. and Tanaka, C. (1991). Dual effect of trimebutine on contractility of guinea pig ileum via the opioid receptors. Gastroenterology 101: 1579–1587.