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Clinical Uses of Gut Peptides

Justin Geoghegan, M.Ch., F.R.C.S.(I),* and Theodore N. Pappas, M.D.†

From Department of General and Visceral Surgery, Friedrich-Schiller University Jena, Jena, Germany; and the Department of Surgery, Duke University Medical Center,† Durham, North Carolina*

Objective
The authors review clinical applications of gut-derived peptides as diagnostic and therapeutic agents.

Summary Background Data
An increasing number of gut peptides have been evaluated for clinical use. Earlier uses as diagnostic agents have been complemented more recently by increasing application of gut peptides as therapeutic agents.

Method
The authors conducted a literature review.

Results
Current experience with clinical use of gut peptides is described. Initial clinical applications focused on using secretomotor effects of gut peptides in diagnostic tests, many of which have now fallen into disuse. More recently, attention has been directed toward harnessing these secretomotor effects for therapeutic use in a variety of disorders, and also using the trophic effects of gut peptides to modulate gut mucosal growth in benign and malignant disease. Gut peptides have been evaluated in a variety of other clinical situations including use as adjuncts to imaging techniques, and modification of behaviors such as feeding and panic disorder.

Conclusions
Gut peptides have been used successfully in an increasing variety of clinical conditions. Further refinements in analogue and antagonist design are likely to lead to even more selective agents that may have important clinical applications. Further studies are needed to identify and evaluate these new agents.

A steadily increasing number of regulatory peptides have been isolated from the gut during the last three decades. The demonstration of a wide range of physiologic and pharmacologic effects of these agents on gut secretomotor function has led to the evaluation of some of these peptides for clinical use. Early applications using secretin, gastrin, and cholecystokinin (CCK) focused on exploiting the secretory and motility effects of these peptides in diagnostic tests.[1,2] More recently, attention has centered on alternative uses including therapeutic applications of gastrointestinal peptides. Modulation of growth in normal and neoplastic tissues, and the possibility of manipulation of gut immune function have generated exciting prospects for the future. Extraintestinal effects of gut-derived pep-

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Address reprint requests to Theodore N. Pappas, M.D., Duke University Medical Center, Box 3479, Durham, NC 27710.
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tides are also being explored, reflecting the dual localization of many of these peptides in the brain as well as the gut, and these are likely to provide novel therapeutic modalities for a variety of disorders. In this article, the current diagnostic and therapeutic applications of gastrointestinal peptides and their synthetic analogues are summarized, and developments in this field that are likely to yield future clinical benefits are also discussed.

SECRETIN

The stimulatory effect of secretin on pancreatic secretion has been used in a range of clinical applications. Its first clinical use was in combination with cholecystokinin in the assessment of pancreatic exocrine secretion.[1] This test required duodenal intubation and its popularity has declined as tubeless tests of pancreatic exocrine have been developed.[3] Secretin continues to be used as an adjunct to radiologic assessment of inflammatory conditions of the pancreas, particularly with ultrasound scanning, but also more recently with magnetic resonance imaging.[4–7] Normally, the main pancreatic duct dilates by about 110% after maximal secretin stimulation. The absence of this response in patients with chronic pancreatitis, caused by periductal fibrosis, has been reported to be highly sensitive in the diagnosis of this disorder.[4] The secretin-ultrasound test has also been promoted as a useful test for selecting patients with pancreas divisum for accessory duct sphincteroplasty. Warshaw et al. have reported excellent specificity (>90%) and sensitivity for the secretin-ultrasound test, although other investigators have been unable to reproduce these excellent results.[8,9] Secretin has also been used to facilitate collection of pancreatic juice at endoscopic retrograde pancreatography (ERCP).[10]

Perhaps the most intriguing clinical application of secretin has been in the diagnosis of Zollinger-Ellison syndrome (ZES). The discovery that intravenous secretin infusion increases gastrin release in patients with ZES revolutionized the diagnosis of this disorder.[11] It still remains the best test for differentiation of ZES from other causes of hypergastrinemia.[12] Romanus et al. showed that the sensitivity of the test is increased by the addition of calcium to the secretin infusion.[13] Selective intra-arterial secretin injection, performed at the time of visceral angiography, combined with hepatic venous sampling for gastrin has emerged recently as one of the most sensitive means of preoperative localization of gastrinomas.[14] Intraoperative secretin testing has also been reported for confirmation of complete excision after targeted resection of macroscopically unidentifiable gastrinoma.[15] Secretin testing also remains important in follow-up of these patients because it can be used to detect subclinical disease recurrence.[16]

A therapeutic role for secretin in the management of intrahepatic cholestasis has been reported in a nonrandomized study of 11 patients. Further evaluation of this therapy is required before it is more widely applied.[17]

GASTRIN

Soon after the amino acid structure of gastrin was sequenced it was shown that almost all of the biologic activity was retained by short sequences of the C-terminal of the parent molecule.[18] Pentagastrin, which is the C-terminal pentapeptide of gastrin, was the first synthetic analogue of a gut peptide to be evaluated for clinical use.[19] After its introduction in 1967, it was used extensively for evaluation of gastric acid secretory function. Hopes that pentagastrin testing of maximal secretory capacity might help in diagnosis of peptic ulcer disease, in selecting patients for operation, and in predicting the likelihood of recurrence all proved unfounded.[20–22] Therefore, it is no longer used in assessment of patients with peptic ulcer disease. Perhaps its only use in evaluation of acid secretion is in the assessment of hypergastrinemia. It is prudent to perform a pentagastrin test to exclude achlorhydria as the underlying cause for hypergastrinemia before proceeding to more sophisticated and expensive investigations. As an alternative to the classical pentagastrin test, pentagastrin may be administered during upper gastrointestinal endoscopy with immediate sampling of gastric juices to screen for hypo- or achlorhydria.[23]

Pentagastrin stimulation has a well-established role in management of medullary carcinoma of the thyroid, although highly sensitive genetic markers have been identified that are likely to replace its use in screening.[24] It is still likely to remain useful in the follow-up of patients after thyroidectomy to detect subclinical recurrent or residual disease.[25]

Gastrin has well-documented trophic effects on the gastric mucosa and possibly also on small and large intestinal mucosa.[26,27] It has also been shown to promote growth of colonic cancer in some experimental models, although considerable controversy has surrounded this issue.[28] Attempts to capitalize on this effect have led to trials of proglumide, a gastrin antagonist, in patients with metastatic colorectal disease. One trial in which proglumide alone was administered to patients with advanced colorectal cancer showed no significant effect[29]; however, in a small Japanese study the addition of proglumide to a standard cytotoxic regime produced a dramatic increase in survival in patients who had undergone resection of hepatic metastatases from colorectal cancer.[30] This latter result suggests that larger studies should be performed to see if there are subgroups of patients (who might possibly be identified by the presence of elevated serum levels of gastrin or by immunohistochemical staining of their tumor tissue for gastrin receptors) who might show a clinically useful tumor response to gastrin antagonists, either alone or in combination with other antineoplastic agents.

Proglumide also antagonizes CCK and studies with more specific antagonists are required to determine if any proglumide effects are related to gastrin or CCK antagonism. The combination of gut peptide agonists or antagonists with standard cytotoxic agents deserves further evaluation as a strategy for the treatment of solid gastrointestinal tumors.

CHOLECYSTOKININ

The stimulatory effect of CCK on gallbladder contraction has been used as a provocation test for the assessment of patients with gallbladder dysmotility syndromes and suspected acalculous biliary disease.[31] In most instances, the gallbladder is imaged by ultrasound after administration of an intramuscular or intravenous dose of CCK. Reproduction of the patient's symptoms or an observed motility defect constitute a positive result. Advocates of the CCK provocation test maintain that it can be used to select patients with acalculous biliary disease who will benefit from cholecystectomy. Early studies supporting this test excluded patients with negative tests from surgery, thus precluding any useful assessment of its predictive value.[32,33] Subsequent studies in which patients with negative CCK provocation tests results also underwent cholecystectomy have shown no difference in outcome between patients with positive and negative test results.[34,35] Measurement of CCK-stimulated gallbladder ejection fraction by hydroxy iminodiacetic acid (HIDA) scintigraphy may be a more sensitive and quantitative means of identifying patients with significant acalculous biliary disease.[36] Further studies are required to confirm the predictive value of this methodology.

The absence of nutrients from the gut lumen in patients treated with prolonged total parenteral nutrition (TPN) reduces release of CCK and other gut peptides. This results in gallbladder hypomotility which promotes biliary sludge formation and TPN-associated cholestasis. Although it is unclear if this impacts on patient outcome in terms of morbidity and mortality, daily administration of CCK has been shown to prevent these complications in both adult and pediatric patient populations.[37,38]

A further consequence of long-term TPN is that gut mucosal atrophy occurs. Intraluminal nutrients contribute to the maintenance of healthy gut mucosa through a number of mechanisms, including release of gut peptides. In dogs administered TPN for a 6-week period, twice daily administration of CCK and secretin prevented the development of intestinal hypoplasia that was seen in animals administered TPN alone.[39] Although not yet established in clinical practice, it seems likely that gut peptides may be used in the future to prevent mucosal atrophy in patients on long-term TPN and possibly to accelerate hypertrophic adaptation in those with short bowel syndrome.

Cholecystokinin may also be important in preservation of the immunologic integrity of the gut. In humans, administration of CCK has been shown to cause an increase in intestinal immunoglobulins.[40] Similar changes have been noted in animal studies along with the demonstration that basal release of these antibodies could be reduced by prior administration of proglumide, a CCK antagonist.[41] This suggests that background tonic stimulation by CCK (and presumably other gut peptides) supports intestinal immunoglobulin production. The role of gut peptides in maintenance of gut mucosal integrity deserves careful evaluation as modulation of these effects may provide a powerful tool for prevention of bacterial translocation in the severely ill surgical patient.

Cholecystokinin has been shown to have trophic effects on a number of gastrointestinal tumor cell lines.[42,43] The development of highly specific CCK antagonists prompted attempts to modulate growth of certain human tumors that commonly express CCK receptors. As yet, no studies have shown any useful effect. In a phase II clinical trial, MK-329 (a CCK-A receptor antagonist) had no effect on patients with advanced pancreatic cancer.[44] It seems logical to apply treatment with gut peptides or their antagonists only to tumors that express specific receptors for that particular peptide. Although it is worth bearing in mind that gut peptides may indirectly affect growth of tumors by altering release of other regulatory peptides that may in turn have trophic effects on the tumor in question. As yet, clinical trials of gut peptides as therapeutic agents for solid gastrointestinal tumors have been confined to patients with advanced disease, in whom it may be difficult to demonstrate benefit from any therapeutic strategy. With further development, hopefully these agents can be evaluated earlier in the course of the disease when they may be more likely to make some impact on patient outcome.

Because of its proven role in the regulation of satiety, considerable interest has focused on the clinical use of CCK in the modulation of feeding behavior.[45,46] Cholecystokinin undoubtedly can reduce food intake and it seems likely that this effect will ultimately be harnessed in a clinically useful manner,[47,48] but further work needs to be done in unravelling the precise site of action of CCK on satiety and the receptor subtypes involved.[49]

The demonstration that CCK is probably also important in the central nervous system in the genesis of panic and anxiety states has generated other possible clinical applications for CCK antagonists.[50,51] Indeed this area may ultimately provide the single most important clinical use for these agents. Administration of CCK-4 has been shown to induce panic attacks in patients with panic disorders and normal volunteers. Preliminary trials suggested that the specific CCK-B antagonist L-365,260 could be of clinical use in patients with panic disorders. However, a recent placebo-controlled trial failed to shown any sig-

nificant benefit.[52] Further studies of this potential application are currently in progress.

GLUCAGON

Glucagon is commonly used in the emergency treatment of accidental insulin-induced hypoglycemia in diabetic patients. Glucagon also causes relaxation of visceral smooth muscle, and this can facilitate radiologic and endoscopic examination of the upper gastrointestinal tract and colon. The lack of cardiac side effects makes it safer than anticholinergic agents that have previously been widely used for this purpose.

The administration of glucagon greatly improves visualization of mucosal detail during hypotonic duodenography.[53] During upper gastrointestinal endoscopy, glucagon may be used to reduce pylorospasm and duodenal contractility, which may be particularly helpful during papillary cannulation at ERCP. Spasm of Oddi's sphincter during intraoperative cholangiography can prevent efflux of contrast into the duodenum, causing concern that a stone may be impacted in the distal common bile duct. Administration of glucagon may relieve the spasm allowing full visualization of the sphincteric portion of the common bile duct. Although up to 2 mg may be administered intravenously, the usual dose required to produce duodenal relaxation is 0.25–0.5 mg. For examination of the colon, 2 mg administered intramuscularly 10 minutes before the procedure produces a more sustained effect.

INSULIN

The discovery of insulin by Banting and Best in 1922 was one of the outstanding breakthroughs in modern medical science.[54] The introduction of insulin radically changed the outlook for patients with diabetes. Consideration of the use of insulin in diabetes is beyond the scope of this article and is not commented on further.

Insulin-induced hypoglycemia is an essential component of the Hollander test for vagal integrity. This test was used extensively used in the late 1960s and early 1970s when clinical measurement of gastric secretion was at the height of its popularity. However, the Hollander test was plagued by misconceptions and difficulties in interpretation and is now largely of historical interest.[55,56] Important concerns were also voiced about the safety of this test and a number of cardiac deaths were associated with its use.[57]

PANCREATIC POLYPEPTIDE

The physiologic role of pancreatic polypeptide is incompletely understood. It is a potent inhibitor of pancreatic exocrine secretion but it may also be important in regulating the hepatic response to insulin, an effect that may prove to be of clinical value. Deficiency of pancreatic polypeptide has been implicated in the glucose intolerance that can result from chronic pancreatitis or pancreatic resection.[58] In animal models and human subjects, there is a decrease in basal and meal-stimulated levels of pancreatic polypeptide after proximal pancreatectomy.[59,60] The diabetic state that occurs in these patients differs from classical diabetes mellitus in that there is hepatic insulin insensitivity, and ocular and vascular complications rarely occur. Human studies have shown that administration of pancreatic polypeptide may reverse the hepatic insulin insensitivity that occurs in these patients, thus ameliorating the glucose intolerance.[58] As the physiologic basis for these observations becomes more clearly understood, pancreatic polypeptide may be applied as part of the treatment of diabetes secondary to chronic pancreatitis or after pancreatic resection.

Measurement of pancreatic polypetide has also been used as a method of assessing vagal integrity.[61] Pancreatic polypeptide is released in a biphasic manner after eating. The first peak is caused by cephalic phase stimulation and the second peak is stimulated by the postprandial increase in blood glucose.[62] The first peak is abolished by vagotomy and attention has focused on this response as the basis for a tubeless test of the completeness of vagotomy. Both modified sham feeding, in which the subject chews food and then spits it out without swallowing, and insulin-induced hypoglycemia cause cephalic-phase pancreatic polypeptide release. Insulin hypoglycemia produces a stronger but less physiologic and specific response than sham feeding. Measurement of the serum pancreatic polypeptide response to sham feeding would seem to be an ideal technique for assessment of vagal integrity. However, in practice only 75% of normal subjects show increased pancreatic polypeptide secretion alter modified sham feeding, limiting its use to patients who have a positive test preoperatively.[62] Another limitation is that highly selective vagotomy has no effect on cephalic-phase pancreatic polypeptide release because pancreatic vagal innervation remains intact. Therefore the use of this test has been confined to a small number of centers.

MOTILIN

The discovery that the gastrointestinal side effects of macrolide antibiotics were related to their activity as motilin agonists uncovered new therapeutic roles for these drugs.[63] In this respect, erythromycin is the most widely studied and used of these agents. Erythromycin increases gastric contractility and emptying, gallbladder emptying, and probably also has an effect on colonic motility.[64–66] It has been shown to be effective in alleviating symptoms caused by gastric stasis in patients with diabetic gastroparesis and systemic sclerosis,[67,68] and to be useful in postoperative surgical patients with slow gastric emptying, par-

ticularly after resection of the head of pancreas and when the stomach is used as an esophageal replacement.[69,70] Erythromycin has also been shown to facilitate fluoroscopically controlled nasoenteric tube placement.[71] Early studies failed to show any effect on colonic motility[72]; however, a recent trial showed that erythromycin increased colonic transit significantly in patients with idiopathic constipation.[66] Future pharmaceutical developments are likely to generate macrolide compounds that retain the prokinetic effects of the currently available agents but have no antibacterial activity.

SOMATOSTATIN

Somatostatin has a broad range of inhibitory effects on secretory function in the stomach, small intestine, pancreas, and liver. It also diminishes gastrointestinal motility and reduces splanchnic blood flow. Early clinical trials using native somatostatin in patients with islet cell tumors showed that this agent could rapidly decrease plasma levels of peptides released by these tumors with concomitant symptomatic improvement.[73,74] Because of its short half-life, somatostatin had to be administered by continuous intravenous infusion. The somatostatin analogue octreotide has a half-life of 90 minutes after subcutaneous injection allowing greater flexibility of treatment, including the possibility of outpatient treatment. The evolution of octreotide serves as a paradigm for future development of analogues of naturally occurring bioactive peptides, retaining as it does all of the desired biological potency of the parent molecule but with a reduced susceptibility to metabolic degradation.

ISLET CELL TUMORS

Based on the successful use of native somatostatin in patients with islet cell tumors, octreotide was first licensed for use in patients with clinical syndromes caused by peptide hypersecretion by neuroendocrine tumors.[75–78] The rarity of these conditions has meant that octreotide has never been subjected to controlled trial and thus the reported experience is largely anecdotal. Nonetheless, a consensus has gradually emerged as to the indications for octreotide treatment in patients with neuroendocrine tumors.

In patients with ZES, octreotide generally lowers gastrin levels effectively. No convincing sustained antitumor effect has been observed in any of the reported studies.[75] Moreover, octreotide is unlikely to become a mainstay of treatment for ZES because of the availability of proton pump inhibitors that so efficiently suppress the end organ damage from hyperacidity in this disease.[12]

Most patients who present with carcinoid syndrome have incurable metastatic disease; before the introduction of octreotide, medical management was unsatisfactory. The diarrhea and flushing associated with carcinoid syndrome typically respond well to octreotide.[77] Carcinoid crisis is particularly responsive to octreotide and it has become established as front line treatment for this situation. Octreotide should be administered prophylactically to patients with carcinoid syndrome who are about to undergo surgery or invasive diagnostic procedures to prevent precipitation of carcinoid crisis.[79]

The severe watery diarrhea associated with vipoma syndrome is effectively controlled by octreotide in approximately 90% of patients. While octreotide is almost invariably successful in ameliorating the diarrhea, it does not always bring about a reduction in the circulating levels of vasoactive intestinal polypeptide.[80,81] This may be so because a variety of other peptides (including neurotensin, pancreatic polypeptide, and motilin) are commonly also secreted by these tumors and the beneficial effect of octreotide may be mediated by a direct effect on these other peptides.

Octreotide has not had a major impact on the treatment of insulinoma because surgical cure is possible in more than 90% of patients. In addition, the effects of octreotide on hypoglycemia in this condition can be unpredictable because glucagon and growth hormone release in response to low blood glucose may also be reduced, thus aggravating the situation.[82] Despite this, a trial of therapy is worthwhile in patients with unresectable malignant insulinoma if symptoms remain poorly controlled.[83] In glucagonoma, octreotide may improve the classic migratory erythematous rash, but usually does not affect the diabetic state.[78]

Octreotide has become established as one the principal treatments for acromegly, and recent studies confirm its safety when used for long-term control of this condition.[84]

IMAGING AND ANTITUMOR EFFECTS

The demonstration of somatostatin receptors on the surface of many tumor cells has stimulated great interest in two possible therapeutic applications for somatostatin and its analogues, namely imaging and direct antineoplastic effects. Iodine 123-tagged octreotide can be used to identify a variety of tumors particularly carcinoid tumors, pheochromocytoma, and paraganglionomas.[85,86] Small cell lung cancer and malignant lymphoma, which may exhibit somatostatin receptors, can also be imaged using variations on this technique.[87,88]

Some of the initial enthusiasm for octreotide usage in islet cell tumors focused on the possibility that it might have a direct antitumor effect. Although initial reports were encouraging, subsequent experience has shown no evidence of any sustained effect in these patients. Octreotide has been used as a vehicle to carry radioisotopes for imaging of tumors that express somatostatin receptors and recently it has been proposed that it may be used to deliver

alpha or beta-emitting radionuclides that could deliver a therapeutic radiation dose.[89] Experience with this approach is limited but objective tumor responses have been observed and further results are awaited.

Octreotide and other somatostatin analogues either alone or in combination with other chemotherapeutic agents have also been evaluated in a variety of other tumors including carcinoma of the pancreas, breast, and prostate.[90–92] None of these studies has shown a significant survival advantage for somatostatin treatment in these diseases, but further trials are continuing. A somatostatin analogue has been shown to have some activity in low-grade non-Hodgkin's lymphoma, and again further studies to validate this result are in progress.[93]

Two small studies have shown significant extension of survival in patients with advanced gastrointestinal cancer that is unresponsive to all other therapies. In one study of patients with advanced pancreatic cancer, octreotide at a dose of 2,000 μg three times per day increased survival from 3 to 6 months.[94] In the second study, mean survival in a group of patients with a variety of gastrointestinal tumors was increased from 11 to 20 weeks using a much lower dose of 200 μg three times per day.[95] It is not clear if these results represent direct antitumor effects of octreotide or are related to suppression of other trophic gut peptides. Clearly further trials are needed to explore these interesting findings. Such trials should include combinations of octreotide with conventional cytotoxic regimes. Octreotide may be useful in palliation of symptoms caused by intestinal obstruction from advanced gastrointestinal cancer. Nausea and vomiting can be significantly reduced in these patients helping with their terminal care.[96]

UPPER GASTROINTESTINAL BLEEDING

An early double-blind study of somatostatin therapy in unselected patients with acute upper gastrointestinal tract bleeding failed to show a clear advantage for this treatment over conventional therapeutic modalities.[97] However, at least four subsequent smaller studies have shown improved outcome with somatostatin in moderate to severe nonvariceal upper gastrointestinal bleeding as measured by transfusion requirement or need for surgery but not overall survival.[98–101]

There have been at least 23 randomized trials in which somatostatin or octreotide therapy has been compared with medical management or sclerotherapy for variceal bleeding.[102–106] In all trials in which somatostatin or octreotide was compared with conventional medical therapies such as vasopressin or propranolol, no significant differences in survival have been demonstrated, although the incidence of side effects has consistently been shown to be significantly lower with somatostatin or octreotide. When compared with sclerotherapy or balloon tamponade, somatostatin or octreotide were once again shown to be equally effective in terms of overall survival, although one trial suggested that octreotide was less effective when active bleeding was seen at endoscopy. Octreotide is likely to become established as an adjunct to endoscopic sclerotherapy because it is at least as effective as vasopressin and balloon tamponade but with a more favorable side-effect profile. Therapy should commence at the time of admission and probably continue for 5 days while the risk of rebleeding is still high.[102]

PROPHYLAXIS FOR ENDOSCOPIC RETROGRADE PANCREATOGRAPHY AND PANCREATIC SURGERY

In several studies somatostatin or octreotide has been administered as prophylaxis against ERCP-induced pancreatitis. Although initial studies suggested that the incidence of post-ERCP hyperamylasemia could be reduced by octreotide, none showed a decrease in the frequency of episodes of pancreatitis.[107] More recent trials have failed to show a benefit for octreotide in this situation and therefore routine administration of octreotide before ERCP or endoscopic sphincterotomy does not seem to be indicated.[108,109]

Two randomized trials have confirmed a significant reduction in the incidence of postoperative complications in patients undergoing elective pancreatic resection. In one, a multicenter Italian study, the incidence of pancreatic fistula was reduced from 19.6% to 9%. The second study showed an equally impressive reduction in the overall morbidity rate in patients receiving octreotide.[110,111] There seems to be be sufficient evidence to support the routine use of octreotide in patients undergoing elective pancreatic surgery.

ACUTE AND CHRONIC PANCREATITIS

Administration of octreotide might be predicted to ameliorate the progress of acute pancreatitis by inhibiting the release of pancreatic enzymes. As with so many candidate therapies for acute pancreatitis, the results from human studies did not produce convincing evidence of benefit, despite encouraging findings in preliminary animal studies.[112,113] Six human studies of somatostatin used in acute pancreatitis individually showed no clear benefit, although a statistically significant result was achieved when these studies were subjected to meta-analysis.[114] There is good evidence that enzyme secretion is usually depressed during acute pancreatitis anyway, so that further secretory suppression by octreotide or somatostatin sufficient to alter the disease process may not be possible. Nonetheless, preliminary results from ongoing trials with octreotide do suggest there may be some real benefit for

octreotide treatment, so for the time being this issue remains unresolved.[115,116]

Two small trials of octreotide use in patients with chronic pancreatitis have produced conflicting results. One showed no reduction in pain,[117] whereas the other study a reduction in analgesic requirement during octreotide treatment.[118] A number of case reports describe a favorable response of pseudocysts associated with chronic pancreatitis to octreotide treatment.[119,120] Further controlled trials are needed to evaluate whether somatostatin or its analogues can reduce the requirement for surgical drainage of pancreatic pseudocysts. Pancreatic ascites has also been reported to respond to octreotide in a limited number of patients.[121]

DUMPING SYNDROME

Dumping syndrome after truncal vagotomy or gastrectomy may occasionally be severe and disabling. Several studies, including one randomized, double-blind, crossover trial, have confirmed the effectiveness of octreotide in controlling dumping symptoms and improving objective measures of dumping such as changes in heart rate and serum insulin levels.[122] Early dumping symptoms are probably relieved by the retarding effect of octreotide on gastric emptying, whereas late dumping symptoms are relieved by blunting of the insulin hypersecretion that occurs in these patients caused by rapid entry of nutrients into the small bowel.[123]

GASTROINTESTINAL FISTULAS

A considerable amount of clinical experience, mostly reported in small, nonrandomized series of patients, has accumulated that vouches for the efficacy of octreotide in reducing output from gastrointestinal fistulas.[124,125] Often a high-output fistula that presents a difficult clinical problem can be converted by octreotide treatment into a low-output fistula that is more easily managed. Despite the claims made for octreotide treatment, it is not clear if octreotide actually accelerates fistula closure or increases the spontaneous fistula closure rate, as many fistulas will close spontaneously without octreotide. Indeed, one small randomized trial of octreotide in patients with postoperative enterocutaneous fistula showed no effect of octreotide on the rate of spontaneous closure.[126] Another randomized trial of octreotide in patients with pancreatic fistula showed no difference in the fistula closure rate, but did show a significant reduction in hospital stay, although, again, the numbers included were small.[127] A randomized trial, large enough to exclude a type II statistical error, is needed to explore these questions rigorously. However, the widely perceived benefit of octreotide in such patients is likely to make it difficult to recruit patients to such a trial.

SECRETORY DIARRHEA

Octreotide may be useful, even life-saving, in a variety of conditions associated with hypersecretory diarrhea in which conventional management options have been exhausted. Mulvihill et al. reported a case of severe life-threatening diarrhea with massive potassium loss that followed decompression of colonic pseudo-obstruction.[128] Diarrhea caused by *Cryptosporidium,* cytomegalovirus, *Giardia,* and other pathogens, in patients with acquired immunodeficiency syndrome may be severe and usually may be controlled with octreotide,[125] as may diarrhea caused by graft versus host disease in transplant recipients.[129]

CONCLUSIONS

Further advancement in biochemical technology will likely lead to the identification of even more biologically active peptides in the gut. One of the great challenges is to increase the specificity of these peptide effects by elucidation of the structure-activity relationships of these peptides and their receptors. This should facilitate design of analogues with more specific activity and improved side-effect profiles. Another important limitation that must be overcome is the mode of delivery of these agents. Intranasal spray is an established administration route for peptide agents and may be more widely used for gut peptides and their related compounds in the future. The application of gut peptides as antineoplastic agents is still in evolution. Evaluation of these agents in early tumors and in combination with standard cytotoxic regimes would seem to be the way forward.

Clearly there is great need for carefully designed clinical trials to provide solid objective evidence for use of these agents. Further basic research is needed to provide a rational basis for such trials. Hopefully, the gastrointestinal tract will continue to be as fruitful a source of "new" bioactive peptides as it has been for the last 90 years, providing us with even more new diagnostic and therapeutic biologic agents.

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