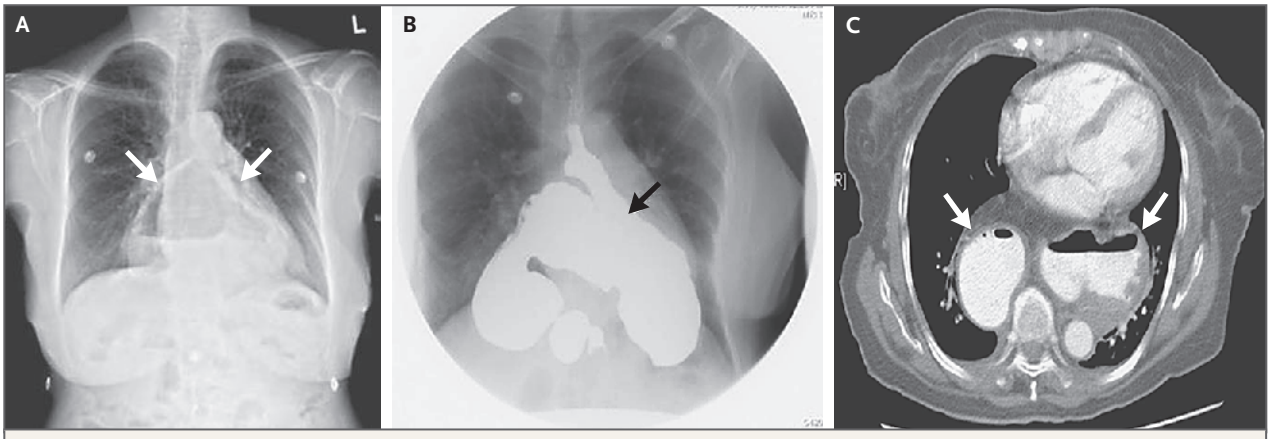

Figure 1. Examinations of the Patient.
Panel A shows the original chest film; 6 years later, a barium study (Panel B) and computed tomography (Panel C) were performed. See the text for explanations of the arrows.

Editor's note: We received 1610 responses, from 85 countries, for this medical mystery. Sixty-two percent of respondents were physicians in practice, 21% were physicians in training, and 12% were medical students. Of the respondents, 65% identified some type of diaphragmatic hernia on the radiograph, which revealed a retrocardiac gastric shadow (Panel A). Specifically, 46% suggested a hiatal hernia, and 13% proposed another type of diaphragmatic defect such as Bochdalek's or Morgagni's hernia; 6% correctly identified gastric volvulus. The remaining 35% of respondents suggested a variety of diagnoses, including aortic aneurysm, Boerhaave's syndrome, Zenker's diverticulum, thymoma, pulmonary abscess, and achalasia.

1. Murali R, Attar BM. A medical mystery: epigastric pain. N Engl J Med 2008;358:1053.

Exenatide and Rare Adverse Events

TO THE EDITOR: Seven years after receiving a kidney transplant, a 44-year old woman with a 31-year history of type 1 diabetes mellitus and long-term complications (retinopathy, neuropathy, and end-stage renal disease) underwent an allogeneic islet-after-kidney transplantation with the use of a modified Edmonton protocol.[1] Islet-graft dysfunction with preserved C-peptide levels was observed after approximately 1 year. After the patient had provided written informed consent, off-label use of exenatide (Byetta, Amylin Pharmaceuticals) (≤10 μg, administered subcutaneously twice daily) was initiated 19 months after the islet transplantation in order to improve glucose control (ClinicalTrials.gov number, NCT00315588).[2] Exenatide treatment resulted in insulin independence and normalization of glycated hemoglobin levels.

Eleven months later, sharp pain developed in the right upper quadrant, along with other symptoms thought possibly to be associated with exenatide treatment: loss of about 11% of body weight, early satiety, nausea, and vomiting.[3] Severe gastroparesis was confirmed with a study of gastric emptying (with the use of radiolabeled meal-tolerance tests). Esophagogastroduodenoscopy showed a 2 cm by 2 cm by 1 cm food-content bezoar, which was safely removed endoscopically. Exenatide treatment was withheld for 1 week after the procedure, and the patient's insulin regimen was adjusted accordingly.

After assessment of the risks and benefits, exenatide was restarted at a lower dose (2.5 μg three times a day), with close surveillance. The patient's condition became clinically stable, and glucose control was optimal. Three months later, gastrointestinal symptoms recurred, and another gastric bezoar was diagnosed and removed by means of esophagogastroduodenoscopy. Exenatide was then discontinued. A follow-up esophagogastroduodenoscopy performed 5 months later showed retained food without the presence of a

well-formed bezoar. Botulinum toxin was endoscopically injected into the pylorus, after which the patient's condition remained stable.

Diabetic gastroparesis may occur in patients with long-standing diabetes mellitus, causing severe gastrointestinal symptoms that may affect the quality of life.[4] Current pharmacologic treatment options are limited, and their success is variable. Exenatide is a glucagon-like peptide 1 (GLP-1) analogue that has potent effects on glucose-dependent insulin release and that also inhibits glucagon secretion and delays gastric emptying. It has been mainly used for the treatment of type 2 diabetes, resulting in significant improvement in glycated hemoglobin levels.[3] In addition, preliminary studies have shown improved glucose control in a selected cohort of patients with type 1 diabetes who had received islet allografts and were treated with exenatide.[2] In patients with gastroparesis, exenatide may cause further delay in gastric emptying, predisposing these patients to bezoars, with the risk of other complications (i.e., obstruction, pancreatitis, and intestinal perforation). A high incidence of pancreatitis has been observed in patients during exenatide treatment.[5] In patients with a history of severe gastroparesis, we recommend careful assessment of the risks and benefits if GLP-1 analogues are being considered as adjuvants for glycemic control.

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Dr. Cure reports holding stock in Amylin Pharmaceuticals. No other potential conflict of interest relevant to this letter was reported.

1. Shapiro AM, Ricordi C, Hering BJ, et al. International trial of the Edmonton protocol for islet transplantation. N Engl J Med 2006;355:1318-30.
2. Ghofaili KA, Fung M, Ao Z, et al. Effect of exenatide on beta cell function after islet transplantation in type 1 diabetes. Transplantation 2007;83:24-8.
3. Heine RJ, Van Gaal LF, Johns D, Mihm MJ, Widel MH, Brodows RG. Exenatide versus insulin glargine in patients with suboptimally controlled type 2 diabetes: a randomized trial. Ann Intern Med 2005;143:559-69.
4. Talley NJ, Young L, Bytzer P, et al. Impact of chronic gastrointestinal symptoms in diabetes mellitus on health-related quality of life. Am J Gastroenterol 2001;96:71-6.
5. FDA alert: information for healthcare professionals — exenatide (marketed as Byetta). Rockville, MD: Food and Drug Administration, 2007. (Accessed April 11, 2008, at http://www.fda.gov/cder/drug/InfoSheets/HCP/exenatideHCP.htm.)

TO THE EDITOR: Exenatide, an incretin mimetic, was approved by the Food and Drug Administration (FDA) on April 28, 2005, as adjunctive therapy to improve glycemic control in patients with type 2 diabetes mellitus. According to the FDA's Adverse Event Reporting System (AERS) database, 48 domestic cases of acute pancreatitis in association with exenatide use have been reported from the date of the drug's approval through December 31, 2006. Reports on 18 cases were excluded (7 cases did not meet the selection criteria, and in 11, there were alternative explanations such as alcohol abuse, cholecystitis, hypertriglyceridemia, hepatitis, and a history of pancreatitis), leaving 30 unique cases for analysis (Table 1).

The median age was 60 years (range, 43 to 72) in the 27 patients for whom age was noted. Nineteen patients (63%) were women. The median dose of exenatide (reported for 25 of the 30 patients) was 10 μg per day (range, 10 to 20; mean, 14). From the initiation of exenatide, the time to the onset of symptoms ranged from 4 to 300 days (median, 34). The serum amylase level, reported in 17 patients, ranged from 40 to 1845 U per liter (median, 384; normal range, 30 to 170). The serum lipase level, reported in 25 patients, ranged from 62 to 16,970 U per liter (median, 545; normal range, 7 to 60). Abdominal pain was reported in 23 patients. In 22 patients, symptoms of pancreatitis began to resolve when exenatide was discontinued; 3 of these 22 patients had a recurrence of symptoms (nausea and vomiting in 2 and abdominal pain in 1) when exenatide was restarted. The diagnosis of acute pancreatitis was supported by findings on computed tomography or ultrasonography in 11 patients. Although there were no reported deaths, serious complications included acute renal failure, suspected ileus, ascites, and phlegmon. Twenty-one patients (70%) required hospitalization. Twenty-seven patients (90%) had at least one other risk factor possibly confounding the association between exenatide and acute pancreatitis; these factors included obesity, hyperlipidemia or hypertriglyceridemia, and alcohol use.

Spontaneous reporting systems are the most common method of pharmacovigilance for identifying new or rare adverse events associated with drug therapy. Incomplete or limited information and underreporting are major limitations of data from the AERS.[1]

It is biologically plausible that exenatide may cause acute pancreatitis, since it is derived from Gila monster venom, which is known to cause pancreatitis in humans.[2] This case series includes one case that has already been published.[3]

On the basis of a review of these cases, the FDA recently asked the manufacturer to strengthen the labeling of acute pancreatitis from the Adverse Reactions section to the Precautions section of the exenatide product label. Health care professionals should be aware of this association and report all serious adverse events to the FDA or the manufacturer.

The views expressed in this letter are those of the authors and do not necessarily represent those of the FDA or the U.S. government.

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1. Ahmad SR, Goetsch RA, Marks NS. Spontaneous reporting in the United States. In: Strom BL, ed. Pharmacoepidemiology. 4th ed. Chichester, England: John Wiley, 2005:135-59.
2. Sherman M. Therapeutic venoms. US Pharm 2005;30:33-6.
3. Denker PS, Dimarco PE. Exenatide (exendin-4)-induced pancreatitis: a case report. Diabetes Care 2006;29:471.

Table 1. Selected Characteristics of 30 Patients with Exenatide-Associated Pancreatitis.*

Variable	Patients with Pancreatitis
Age	
Range — yr	43–72
Median — yr	60
Mean — yr	58
Not reported — no.	3
Sex — no. (%)	
Female	19 (63)
Male	11 (37)
Daily dose	
Range — μg/day	10–20
Median — μg/day	10
Mean — μg/day	14
Not reported — no.	5
Time to onset of symptoms	
Range — days	4–300
Median — days	34
Mean — days	53
Not reported — no.	1
Outcome at time of report submission — no.	
Patient had not recovered	2
Patient had recovered	22
Not reported	6
Serum amylase level	
Range — U/liter	40–1845
Median — U/liter	384
Mean — U/liter	508
Normal range — U/liter	30–170
Not reported — no.	13
Serum lipase level	
Range — U/liter	62–16,970
Median — U/liter	545
Mean — U/liter	1610
Normal range — U/liter	7–60
Not reported — no.	5

* The 30 cases of pancreatitis were reported by the Adverse Event Reporting System from April 28, 2005, through December 31, 2006.

AMYLIN PHARMACEUTICALS, THE MANUFACTURER OF EXENATIDE, OFFERS THE FOLLOWING REPLY: We would like to clarify certain aspects of the letters from Cure et al. and Ahmad and Swann. Cure et al. describe a patient with type 1 diabetes and gastroparesis in whom a bezoar developed during treatment with exenatide. It should be emphasized that exenatide is not indicated for patients with type 1 diabetes and is not recommended for patients with severe gastrointestinal disease, including gastroparesis. Although diabetes can result in autonomic neuropathy and gastroparesis, we are aware of only one additional spontaneously reported case of a bezoar in a patient who was receiving exenatide; the patient underwent surgery and recovered. There were no reports of bezoars during clinical trials of exenatide.

Ahmad and Swann discuss an association be-

tween exenatide and pancreatitis and state, "It is biologically plausible that exenatide may cause acute pancreatitis, since it is derived from Gila monster venom, which is known to cause pancreatitis in humans." In fact, exenatide is unrelated to Gila monster (*Heloderma suspectum*) venom, and there are no published cases of pancreatitis after the bite of a Gila monster. Rather, exenatide is a synthetic version of exendin-4, a protein expressed in the salivary glands of the Gila monster (common collection techniques capture both fluids).[1,2] Exendin-4 circulates at high levels before and during feeding to prepare the Gila monster for large and infrequent nutrient loads.[3,4] Preclinical studies using exenatide doses that exceeded those used in clinical practice by a factor of more than 100 and that were given for several months did not result in pathological changes in the pancreas.

As described in a U.S. "Dear Healthcare Professional" letter in October 2007 and on the updated U.S. label for exenatide,[5] postmarketing cases of acute pancreatitis have been reported in patients treated with exenatide. On the basis of spontaneous reporting, the rate of pancreatitis as of December 2007 is 0.27 event per 1000 patient-years. Finally, Ahmad and Swann correctly state that there were no deaths in their reported cases of pancreatitis. Since their review, cases with a fatal outcome involving pancreatitis have been reported at a rate that is similar to that expected in the general population of patients with pancreatitis.

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1. Chen YE, Drucker DJ. Tissue-specific expression of unique mRNAs that encode proglucagon-derived peptides or exendin 4 in the lizard. J Biol Chem 1997;272:4108-15.
2. Russell FE, Bogert CM. Gila monster: its biology, venom and bite — a review. Toxicon 1981;19:341-59.
3. Christel CM, Denardo DF. Release of exendin-4 is controlled by mechanical action in Gila monsters, Heloderma suspectum. Comp Biochem Physiol A Mol Integr Physiol 2006;143:85-8.
4. Christel CM, Denardo DF, Secor SM. Metabolic and digestive response to food ingestion in a binge-feeding lizard, the Gila monster (Heloderma suspectum). J Exp Biol 2007;210:3430-9.
5. Byetta. San Diego, CA: Amylin Pharmaceuticals, 2007 (package insert).