

# Rapid Endoscopic Secretin Stimulation Test and Discrimination of Chronic Pancreatitis and Pancreatic Cancer From Disease Controls

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**Background & Aims:** The cholecystokinin (CCK)/secretin pancreatic function tests to diagnose pancreatic exocrine insufficiency are time consuming and invasive. Our aim was to develop a rapid pancreatic function test performed during upper endoscopy that could discriminate between patients with normal from impaired exocrine pancreatic secretion. **Methods:** We prospectively evaluated 412 patients for possible pancreatic diseases. During upper endoscopy, 1 CU/kg of secretin was given intravenously and duodenal juice (collected for 10 min) was assayed for concentrations of bicarbonate and lipolytic and trypsin activity. Final diagnosis was by histology, imaging, and a previously validated scoring system (for chronic pancreatitis). Of 412 patients, 117 patients had normal pancreas, 72 patients had chronic pancreatitis, and 116 patients had pancreatic adenocarcinoma. The remaining 107 patients had miscellaneous disease of the peripancreatic region. In 28 patients we also validated the secretin test with the standard CCK pancreatic function test. **Results:** There was no difference between bicarbonate or trypsin concentrations among the groups. Lipolytic concentration was significantly lower in chronic pancreatitis ( $115 \pm 18$ ) and in pancreatic adenocarcinoma ( $87 \pm 10$ ) compared with patients with normal pancreas ( $229 \pm 23$ ;  $P < 0.03$  and  $P < 0.0001$ , respectively). The overall accuracy of the endoscopic secretin test was 79%, with positive and negative predictive values of 73% and 85%, respectively. The concentration of lipolytic activity obtained by the endoscopic secretin test in 28 patients correlated moderately well ( $r = 0.41$ ,  $P < 0.03$ ) with lipolytic output obtained by the CCK pancreatic function test. **Conclusions:** Lipolytic concentration in duodenal juice after intravenous secretin collected for 10 minutes during upper endoscopy was significantly lower in chronic pancreatitis and pancreatic adenocarcinoma compared with patients with normal pancreas, but was not accurate enough for routine clinical use.

sensitive in detecting fine morphologic changes of the pancreas that might be found in early chronic pancreatitis (absence of steatorrhea, calcification, or diabetes mellitus). Endoscopic ultrasonography may distinguish among focal or diffuse parenchymal changes, increased or decreased echo texture of the gland, and, in more advanced cases, calcifications, lobulations, and bands of fibrosis.<sup>1,2</sup> However, morphologic changes visualized by endoscopic ultrasonography may or may not be related to chronic pancreatic inflammation. The gold standard of pancreatic function, cholecystokinin (CCK), and secretin tests are 90% sensitive and specific, but require duodenal intubation, are time consuming, and are uncomfortable for some patients. Some use combined ERCP and a CCK/secretin test to diagnose early pancreatitis because the latter is a better indicator of histologic changes in chronic pancreatitis.<sup>3,4</sup> Therefore, there continues to be a search for a feasible, inexpensive, and routinely available test to discriminate patients with early exocrine pancreatic dysfunction from persons with a normal pancreas. We<sup>5</sup> and others<sup>6-8</sup> have developed more simple, abbreviated versions of direct pancreatic function tests that are performed concurrently with upper gastrointestinal endoscopy. Their use as accurate tests of exocrine pancreatic function, however, is uncertain, particularly because some tests have a great overlap of values between groups of patients and require 40 minutes to complete.<sup>6-8</sup> Our aims, therefore, were to develop a rapid (10 min) and accurate test of pancreatic function that could be performed during routine upper endoscopy using secretin stimulation and to validate this endoscopic secretin test with the CCK gold standard pancreatic function test.

The early diagnosis of diseases of the exocrine pancreas is challenging, but direct function tests may be abnormal before imaging tests. For example, transabdominal ultrasonography, computed tomography, and endoscopic retrograde pancreatography (ERCP) are in-

**Abbreviations used in this paper:** CCK, cholecystokinin; ERCP, endoscopic retrograde pancreatography.

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**Table 1.** Diagnostic Scoring System for Chronic Pancreatitis

Criterion	Score
Pancreatic calcification	
Definite	4
Probable	2
Histology	
Definite	4
Probable	2
Lipase output (<77 Ku/h) or steatorrhea	2
Pancreatic duct abnormalities at ERCP or computed tomography (also calcifications)	3
Major clinical criteria upper abdominal pain or weight loss >10 kg in 12 months	2
Diabetes (fasting glucose >140 mg/dL)	1

NOTE. Total score  $\geq 4$  for chronic pancreatitis. Data from references 9 and 10.

## Materials and Methods

We evaluated 412 consecutive patients who were referred to the pancreas clinic of the Mayo Clinic between March 1995 and December 1998 for evaluation of a possible pancreatic disorder. The Institutional Review Board of the Mayo Clinic approved this study and all patients gave written informed consent before entering the study. The final diagnosis was made by surgery and/or histology in 183 patients and by combination of imaging tests such as computed tomography, ERCP, and endoscopic ultrasonography in 229 patients. The diagnosis of chronic pancreatitis was made by using a scoring system based on morphologic and functional criteria (Table 1), as previously validated in a cohort of 416 patients with chronic pancreatitis of various causes<sup>9</sup> and also described in other studies<sup>10</sup>; (score  $\geq 4$  required for the diagnosis of chronic pancreatitis). We did not use endoscopic ultrasonography to diagnose chronic pancreatitis in this study.

After overnight fasting, all patients underwent routine upper endoscopy with standard sedation (combination of midazolam and meperidine). Immediately before intubation, 1 CU/kg (maximum dose, 70 CU) of secretin was given intravenously over 1 minute. According to the manufacturer (Ferring Pharmaceuticals AB, Malmo, Sweden), 1 mg of the peptide secretin corresponds to approximately 3,000 CU. In this study we used up to 70 CU per patient. This dose is equal to 23 mcg. If fluid was present in the stomach, this was suctioned before collection of the pancreatic secretions. After the endoscope was placed in the second portion of the duodenum, a disposable washing aspiration catheter (7 F, 240 cm in length; Wilson-Cook, Winston-Salem, NC) was introduced through the biopsy channel of the endoscope to collect the pancreatic juice exiting the papilla of Vater. No cannulation of the papilla was performed. Fluid was collected until at least 25 mL was collected or 10 minutes had elapsed. The fluid was placed immediately in ice. Lipolytic, trypsin concentrations, and bicarbonate (back titration) were analyzed by pH-stat titrator, as previously described.<sup>11</sup>

## Validation Test

The patients who had a CCK pancreatic function test were selected on a clinical basis, usually because they had less evident chronic pancreatitis. Eight of 13 patients with chronic pancreatitis (of the entire group of 28 who underwent the CCK test) had a negative computed tomography scan. Further, these 13 patients with chronic pancreatitis had less severe chronic pancreatitis according to the scoring system than the other 59 patients with chronic pancreatitis (score, 5.4 vs. 6.7,  $P < 0.04$ ). The nonpancreatic disease patients who had the CCK test were selected to have the test because of symptoms including abdominal pain, weight loss, and diarrhea.

The CCK pancreatic function test was performed on a different day in 28 of 412 patients (13 with chronic pancreatitis and 15 with a normal pancreas). For this test, gastroduodenal and orogastric tubes were placed under endoscopic and/or fluoroscopic guidance. After placement of the tubes, a nonabsorbable marker, polyethylene glycol (PEG), was infused into the duodenum as previously described.<sup>11-13</sup> CCK-octapeptide (OP) was administered intravenously at a rate of 40 ng/kg/hr for 1 hour. Duodenal samples were collected every 20 minutes and enzyme (lipolytic and trypsin) concentrations were measured by pH-stat titrator assay. Our established normal ranges for trypsin and lipolytic output were 25.3–54.2 and 77.2–322  $\times 1000$  U/h, respectively.<sup>11-13</sup>

## Statistical Analysis

Analysis of variance with the post-hoc Bonferroni correction was used to calculate differences of lipolytic and trypsin activities among groups. Regression analysis was used to correlate enzyme output (standard CCK test) to enzyme concentration (endoscopic secretin test). A  $P$  value  $< 0.05$  indicated statistical significance.

## Results

There were 214 men and 198 women; the mean age was 59.3 years (range, 17–89 yr) (Table 2). The final diagnosis was no pancreatic disease in 117 patients; post-acute pancreatitis in 27 patients (patients with at least one attack of acute pancreatitis who had recovered and were being evaluated for chronic pancreatitis); chronic pancreatitis in 72 patients; pancreatic ductal adenocarcinoma in 116 patients; other malignant pancreatic tumors such as intraductal papillary mucinous tumor with invasive cancer, mucinous cystadenocarcinoma, and islet cell carcinoma in 11 patients; benign pancreatic tumors such as serous cystadenoma and intraductal papillary mucinous tumor adenoma in 31 patients; islet cell tumors in 10 patients; periampullary tumors other than pancreatic (ampullary, duodenal [second and third part of the duodenum], biliary) in 23 patients; and simple pancreatic cysts in 5 patients.

The average amount of fluid collected was 22 mL (range, 3–53 mL) with no differences among all groups

**Table 2.** Patients' Demographics With Mean Values of Lipase and Trypsin Concentrations

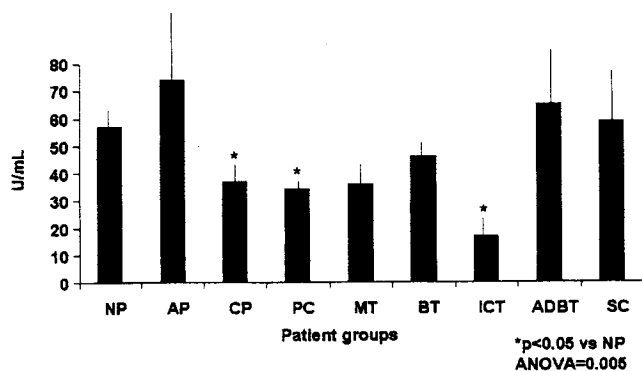
Patient group	No. of patients (n = 412)	Men/women	Mean age (range in yr)	Lipase (U/mL ± SE)	Trypsin (U/mL ± SE)
Normal pancreas	117	55/62	55.7 (17-89)	223.5 ± 25.2	56.6 ± 5.8
Post acute pancreatitis	27	10/17	52.3 (20-80)	221.2 ± 56.4	73.9 ± 24.9
Chronic pancreatitis	72	42/30	53.9 (18-89)	115.4 ± 18.2 <sup>a</sup>	37.1 ± 4.9 <sup>a</sup>
Pancreatic ductal adenocarcinoma	116	72/44	64.3 (32-82)	86.7 ± 10.1 <sup>a</sup>	34.3 ± 3.7 <sup>a</sup>
Malignant pancreatic tumors	11	5/6	63.6 (41-75)	109.8 ± 30 <sup>a</sup>	36.1 ± 8.4
Benign pancreatic tumors	31	15/16	68.7 (49-84)	168.7 ± 34.3	46 ± 6.4
Islet cell tumors	10	5/5	49.1 (29-73)	78.8 ± 22.7 <sup>a</sup>	16.8 ± 4.9 <sup>a</sup>
Ampullary, duodenal, biliary tumors	23	11/12	67.6 (42-87)	201.9 ± 72.4	64.9 ± 20.2
Simple pancreatic cysts	5	1/4	65.6 (28-77)	166.9 ± 79.8	58.6 ± 18.6

<sup>a</sup>Significantly less compared with patients without pancreatic disease.

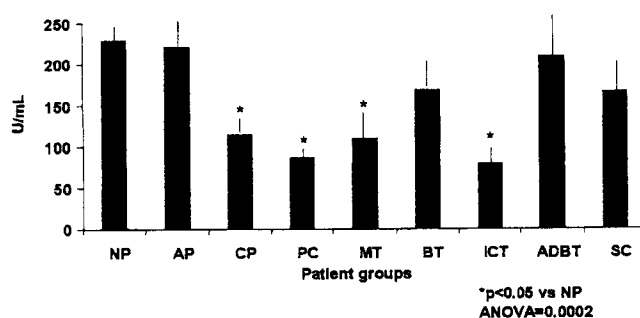
of patients. No complications were observed during the 412 secretin stimulation tests. Bicarbonate analysis was performed by back titration in 96 of 412 patients. All but 1 patient, including subjects in all categories, had less than 80 mEq/L. Most patients had a concentration less than 40 mEq/L, and there was no significant difference among groups. Trypsin concentration in response to secretin was significantly lower for patients with chronic pancreatitis, pancreatic ductal adenocarcinoma, and islet cell tumors when compared with patients without pancreatic disease (Table 2, Figure 1,  $P < 0.05$ , analysis of variance [ANOVA] 0.005). Similarly, lipolytic concentration in response to secretin was significantly lower for patients with chronic pancreatitis, pancreatic ductal adenocarcinoma, malignant pancreatic tumors, and islet cell tumors when compared with patients without pancreatic disease (Table 2, Figure 2,  $P < 0.05$ , ANOVA 0.0002). Among the chronic pancreatitis patients there was an expected negative correlation between the con-

centration of lipolytic activity and the score of chronic pancreatitis ( $r = 0.24$ ;  $P < 0.05$ ).

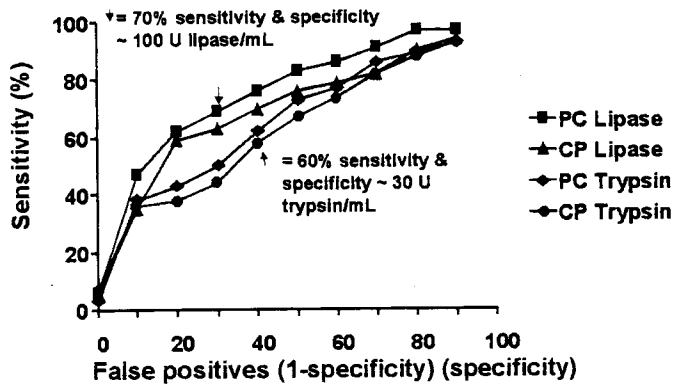
To determine the best sensitivity and specificity values and the best single quantitative index of the diagnostic accuracy for lipolytic and trypsin concentrations obtained with the endoscopic secretin test, we constructed receiver operating characteristic curves for patients with chronic pancreatitis and pancreatic adenocarcinoma (Figure 3). From these curves, we concluded that 70% sensitivity and 70% specificity for lipase was the best discriminator for differentiating chronic pancreatitis and pancreatic ductal adenocarcinoma from normal pancreas. The concentration of lipolytic activity at this sensitivity and specificity was 104 U/mL. The best discriminating sensitivity and specificity for trypsin was lower (60%) and the trypsin concentration at this sensitivity and specificity was 30 U/mL. Thus, lipolytic concentration discriminated chronic pancreatitis and pancreatic cancer from no pancreatic disease better than trypsin concentration. However, at the cut-off value of the lipolytic concentra-



**Figure 1.** Trypsin concentration in response to secretin. Significantly less trypsin concentration was detected in patients with chronic pancreatitis, pancreatic adenocarcinoma, and islet cell tumors when compared with patients with normal pancreas. NP, normal pancreas; AP, acute pancreatitis; CP, chronic pancreatitis; PC, pancreatic ductal adenocarcinoma; MT, malignant pancreatic tumors; BT, benign pancreatic tumors; ICT, islet cell tumors; ADBT, ampullary, duodenal, biliary tumors; SC, simple pancreatic cysts.



**Figure 2.** Lipase concentration in response to secretin. Significantly less lipolytic activity was detected in patients with chronic pancreatitis, pancreatic adenocarcinoma, other malignant pancreatic tumors, and islet cell tumors when compared with patients with a normal pancreas. NP, normal pancreas; AP, acute pancreatitis; CP, chronic pancreatitis; PC, pancreatic ductal adenocarcinoma; MT, malignant pancreatic tumors; BT, benign pancreatic tumors; ICT, islet cell tumors; ADBT, ampullary, duodenal, biliary tumors; SC, simple pancreatic cysts.

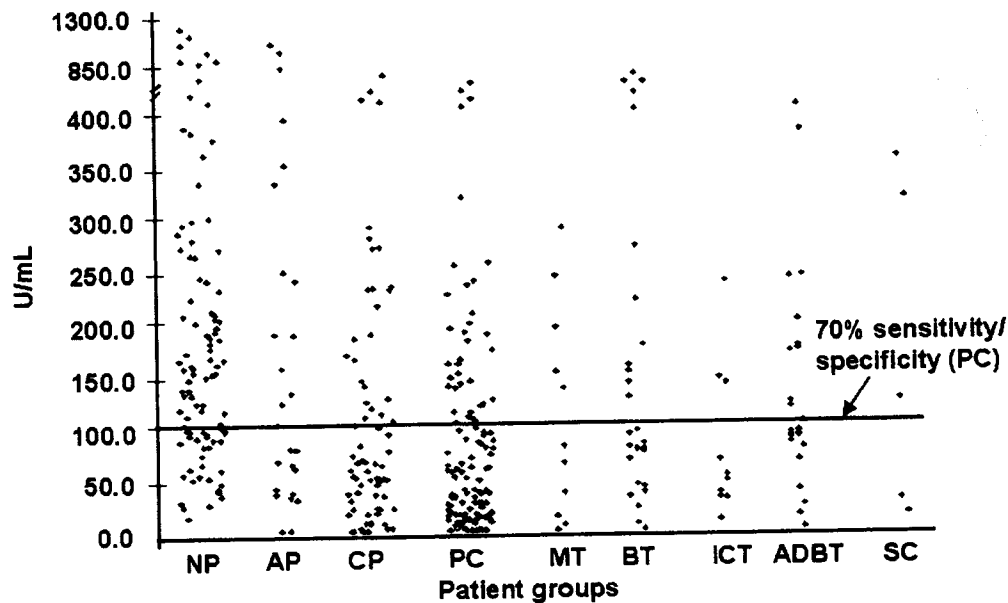


**Figure 3.** Receiver operating characteristics curve for lipase and trypsin concentration in patients with chronic pancreatitis (CP) and pancreatic adenocarcinoma (PC). The best sensitivity and specificity values for lipase (100 U/mL) and trypsin (30 U/mL) concentrations were 70% and 60%, respectively.

tion of 104 U/mL there was a substantial overlap of the lipolytic concentration among patients with chronic pancreatitis or pancreatic ductal adenocarcinoma when compared with patients without pancreatic disease (Figure 4).

#### Correlation of Output (CCK Test) With Concentration (Endoscopic Secretin Test) of Lipolytic Activity

In the chronic pancreatitis group, 11 patients had a negative computed tomography scan of the pancreas.

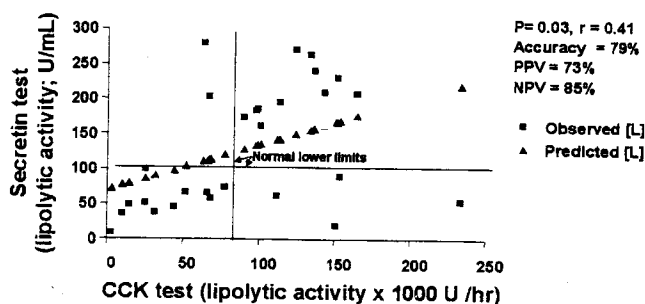


**Figure 4.** Distribution of lipase concentration in response to secretin. The horizontal line is the lipase concentration of 104 U/mL, which is the concentration for the best sensitivity and specificity of 70% to discriminate pancreatic adenocarcinoma from no pancreatic disease. There was substantial overlap of lipase concentration among patients with chronic pancreatitis and pancreatic adenocarcinoma when compared with patients without pancreatic disease. NP, normal pancreas; AP, acute pancreatitis; CP, chronic pancreatitis; PC, pancreatic ductal adenocarcinoma; MT, malignant pancreatic tumors; BT, benign pancreatic tumors; ICT, islet cell tumors; ADBT, ampullary, duodenal, biliary tumors; SC, simple pancreatic cysts.

Of these, 8 had a CCK test (all with an abnormal test result). Indeed, the patients who had the CCK test had a lower score compared with the score of the remaining patients with chronic pancreatitis (score, 5.4 vs. 6.7;  $P < 0.04$ ), indicating a less severe disease by the scoring system. The concentration of lipolytic activity obtained by the endoscopic secretin test in 28 patients (13 with chronic pancreatitis and 15 with no pancreatic pathology) correlated moderately well ( $r = 0.41$ ,  $P < 0.03$ ) with lipolytic output obtained by the CCK-OP pancreatic function test (Figure 5). The overall accuracy of the endoscopic secretin test was 79%, with positive and negative predictive values of 73% and 85%, respectively.

#### Discussion

We found that concentration of lipolytic activity obtained during routine upper endoscopy after secretin stimulation was significantly lower in patients with chronic pancreatitis and pancreatic ductal adenocarcinoma than in patients without pancreatic disease. In addition, lipolytic concentration correlated moderately well with lipolytic output during a gold standard CCK-OP pancreatic function test. Trypsin concentration correlated less well than lipolytic concentration, particularly during the validation test (data not shown), and bicarbonate concentration was not different among all patient groups studied.



**Figure 5.** Comparison between CCK (output) and secretin test (concentration) in 28 patients. The observed lipase compared favorably with the predicted one ( $P < 0.03$ ,  $r = 0.41$ ).

The endoscopic secretin test was simple, safe, and rapid to perform. This test added 10 minutes to the total time needed for a routine upper endoscopy. However, this test was only relatively accurate, with a sensitivity and specificity of 70%. Although it is potentially widely applicable in the diagnostic work-up of patients with a suspicion of pancreatic diseases, it is not as accurate as the gold standard CCK test and therefore cannot be used as a gold standard test presently. A normal test is 80% accurate, but an abnormal test is only 75% accurate.

There are several potential limitations of this exploratory study. Initially, we decided to use secretin and not CCK because we wanted to combine pancreatic function testing and pancreatic cytology by using the same samples. We judged that a satisfactory sample for cytology should consist of relatively uncontaminated pancreatic juice, best obtained by using secretin. Also, although using CCK would have generated pancreatic enzyme concentrations similar to the results of the standard CCK test, others reported that lipase and bicarbonate concentrations in pancreatic juice obtained from the pancreatic duct during ERCP and after secretin stimulation were useful in evaluating exocrine pancreatic function.<sup>14</sup> Perhaps surprisingly, we found that bicarbonate concentrations were low and were not significantly different among groups of patients. We suspect this result is owing to the short duration of juice collection; peak concentration of bicarbonate during the standard secretin test occurs much later. In addition, exocrine pancreatic function decreases in the elderly.<sup>15-17</sup> However, there was no significant difference in age among the disease groups compared with patients without pancreatic disease (mean age, 58 yr). Lastly, it is possible that meperidine and midazolam, which were used for sedation before endoscopy, may have decreased or delayed pancreatic secretion. Opiates might reduce and delay pancreatic exocrine function via the cholinergic pathway.<sup>18,19</sup> If midazolam affects exocrine pancreatic secretion, it is unknown, but

diazepam with hyoscine butylbromide delays the secretion of trypsin into the duodenum.<sup>20,21</sup> These data suggest that the sedation used in this study may have affected exocrine secretion. However, it is unlikely that the sedation affected the comparison of the disease groups with the control group of normal pancreas because all subjects in this study received both midazolam and meperidine.

Recombinant secretin is now available to test for pancreatic function. In a study by Somogyi et al.,<sup>22</sup> the accuracy of synthetic porcine secretin in diagnosing pancreatic insufficiency was 100% when compared with biologic porcine secretin. It behaves just as the old secretin in terms of pancreatic secretion, albeit at different doses. Therefore, results with the synthetic secretin should not differ significantly from our results.

Technical improvements of the endoscopic secretin test or investigating other substances in pancreatic secretion might increase the accuracy of this test. Examples of such substances are indicators of inflammation, a common development accompanying most diseases of the exocrine pancreas. Already it has been reported that concentrations of interleukin 8 were increased in the pancreatic juice obtained by aspirating the pancreatic duct of patients with chronic pancreatitis.<sup>23</sup>

Another substance that deserves some consideration is transforming growth factor  $\beta$  because it stimulates the synthesis of extracellular matrix components and inhibits matrix degradation, resulting in tissue repair and fibrosis.<sup>24</sup> It is up-regulated in chronic pancreatitis. Normally it localizes to distal ductules and enteroacinar cells, but in chronic pancreatitis it localizes to the panductular region.<sup>25</sup> Recently, some investigators reported increased concentrations of transforming growth factor  $\beta$  in pure pancreatic juice after cannulation during ERCP in patients with chronic pancreatitis.<sup>26</sup>

Ideally, a test that combines pancreatic function with pancreatic morphology with acceptable sensitivity and specificity values might be the most reasonable diagnostic approach to discriminate patients with pancreatic disease from patients with no pancreatic pathology. The best combination of tests for this purpose might be a rapid endoscopic secretin test of pancreatic function with endoscopic ultrasound of the pancreas, which in the future may be the screening test for evaluation of possible chronic pancreatitis. Alternatively, magnetic resonance pancreatography with secretin stimulation and measuring pancreatic secretion by assessing duodenal filling<sup>27-29</sup> could be used as a noninvasive test, particularly when there are contraindications for endoscopy.

In summary, the endoscopic secretin test we describe is a rapid test of exocrine pancreatic function that can be performed during endoscopy with little added time and effort. The features of simplicity, speed, and broad applicability (it can be performed by any endoscopist with access to a laboratory that measures enzymes), make the test very attractive. Our test differs significantly from that described by Conwell et al.<sup>6-8</sup> The secretin test takes only 10 minutes as compared with the 40-minute test described by Conwell et al. We believe it is unlikely that a test that takes 40 minutes to collect juice will be accepted widely by endoscopists.

We make no claims that the endoscopic secretin test is ready for clinical use. In comparison with the gold standard CCK-OP test in a significant number of patients, we found that the test results correlate significantly but not strongly enough to suggest that the secretin endoscopic test can replace the CCK-OP test as the gold standard. Our overall results, obtained from study of a large cohort, and the data of Conwell et al.,<sup>6-8</sup> obtained from a much smaller cohort, do not support using these endoscopic tests for assessment of exocrine pancreatic function in individual patients. We conclude the tests are not sensitive enough to confidently detect pancreatic disease in an individual person because there is too large an overlap of values among normal persons and patients with diseases of the pancreas. The ease of performing the secretin endoscopic test and the possibility of combining this test with endoscopic ultrasound, however, makes it attractive for the general gastroenterologist to use in clinical practice. If this is done, we stress that the practitioner should keep in mind that normal and abnormal test results are 80% and 75% accurate, respectively. Therefore, the result of the test may not absolutely predict the diagnosis of pancreatic insufficiency. Nevertheless, although no comparison was made, the secretin endoscopic test may be far superior to the tubeless tests of pancreatic function. In addition, the accuracy of the test may increase with technical improvements, such as adding measurements of markers of inflammation or neoplasia.

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