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EDITORIAL

Where Have All the Dreiling Tubes Gone?

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The direct measurement of pancreatic function remains the best tool for diagnosing chronic pancreatitis, especially if imaging tests are normal or inconclusive. The most effective means of measuring pancreatic function is the standard hormone stimulation test using secretin. Traditionally, direct pancreatic function testing involves the fluoroscopic placement of an oroduodenal tube and collection of duodenal fluid containing pancreatic secretions after administration of a standardized dose of secretin and/or CCK. The test is time-consuming and tedious to perform, and placement of the oroduodenal tube is often difficult for the person performing the test and uncomfortable for the patient. Bicarbonate concentration typically has been measured by back-titration, requiring specialized equipment no longer found in most hospital clinical chemistry laboratories. For these reasons, the direct testing of pancreatic function after secretin stimulation has become a much admired but rarely performed test, currently done in only a few centers in the United States. In this issue of the *Journal*, Stevens *et al.* report on a cross-over study of secretin-stimulated endoscopic pancreatic function test (ePFT) and dreiling tube pancreatic function test (D-PFT) in healthy subjects and demonstrate that the accuracy of the ePFT is comparable to that of the D-PFT (17). They have demonstrated the relative simplicity and reliability of ePFT, bringing it closer to the diagnostic armamentarium of the practicing physician. We may have lost the Dreiling tube but, in its place, gained a "gold standard" which will be more widely used.

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The direct measurement of pancreatic function remains the best tool for diagnosing chronic pancreatitis, especially if imaging tests are normal or inconclusive (1). The most effective means of measuring pancreatic function is the standard hormone stimulation test using secretin (2). This test has withstood the test of time and continues to be the "gold standard," given the inability to routinely assess pancreatic histology. A number of studies have confirmed this type of testing as the most sensitive (up to 90%) and specific (up to 90%) test in the diagnosis of chronic pancreatitis (1–7). This is particularly true in the subset of patients with absent or equivocal structural changes. Although no completely uniform relationship between abnormal structure and function exists, imaging studies often lack the sensitivity to identify patients with "small duct" disease.

Traditionally direct pancreatic function testing involves the fluoroscopic placement of an oroduodenal tube and collection of duodenal fluid containing pancreatic secretions after administration of a standardized dose of secretin and/or cholecystokinin (CCK). In a combined secretin-CCK test, enzymes such as trypsin, amylase, or lipase as well as bicarbonate can be measured (8–10). There is general agreement that the secretagogues should be given to provide maximal stimulation of the pancreas. Although the combined use of secretin and CCK may improve test sensitivity, specificity suffers (2).

The most accurate and least variable measurement has been the peak bicarbonate concentration (1, 2, 4, 5). If the bicarbonate concentration reaches 80 mEq/L in any of the four 15-min collection periods after stimulation with secretin, pancreatic function is considered normal. However, the test's accuracy depends on an adequate collection of duodenal fluid containing pancreatic secretion and on the ability to measure bicarbonate concentration accurately in the collected fluid. The test is time-consuming and tedious to perform, and placement of the oroduodenal tube is often difficult for the person performing the test and uncomfortable for the patient. Bicarbonate concentration typically has been measured by back-titration, requiring specialized equipment no longer found in most hospital clinical chemistry laboratories. For these reasons, the direct testing of pancreatic function after secretin stimulation has become a much admired but rarely performed test, currently done in only a few centers in the United States (2).

Due to the difficulties inherent in performing this "gold standard" test, a number of simpler noninvasive tests have been devised over the years. These include

1. indirect tests of pancreatic enzyme activity (*e.g.*, bentiromide test, pancreolauryl test, fecal fat determination); and
2. measurement of pancreatic enzymes (*e.g.*, serum trypsin, fecal chymotrypsin, fecal elastase).

Although these "tubeless" tests are relatively inexpensive, easily performed, and essentially risk-free, there have been problems due to lack of reproducibility and, especially, sensitivity for diagnosing patients with mild-to-moderate chronic

pancreatitis (2, 11). Because of these limitations, the bentiromide test is no longer available in the United States; and the pancreolauryl test has never been approved for use in this country.

Although pancreatic imaging tests have been considered insensitive in early or mild chronic pancreatitis (1, 2), one more recent modality deserves mention. Endoscopic ultrasound (EUS) diagnosis of chronic pancreatitis appears to be accurate when at least five criteria of parenchymal or ductal changes associated with chronic pancreatitis are observed (12, 13). Secretin-stimulated EUS may enhance the ability to diagnose chronic pancreatitis but has not been widely used and requires further study (14). As EUS moves out from specialty centers and becomes increasingly available in the community, more and more patients with chronic abdominal pain and normal abdominal CT and MRI evaluations of the pancreas are being diagnosed with chronic pancreatitis based on EUS findings alone. This is cause for considerable concern because some of the EUS criteria are subtle and, to some degree, subjective; and endoscopists performing EUS do not always carefully list the criteria for chronic pancreatitis they believe are present which support a common procedure report impression, "findings consistent with chronic pancreatitis." A reliable, easy to perform, direct test of pancreatic function would be of invaluable assistance in further evaluating patients with equivocal EUS findings for chronic pancreatitis or for whom EUS results appear to be inconsistent with the clinical course or other imaging findings.

Over the years, several modifications have been made of the original oroduodenal tube introduced in 1908 by Einhorn (15). Agren and Lagerlof made an important advance in 1936 by designing a tube with two lumens, one with gastric aspiration ports and the second with ports in the duodenum (15). This allowed gastric secretions containing hydrochloric acid to be removed so that they would not neutralize bicarbonate if they reached the duodenum. This was later modified by Dreiling and Hollander in 1948 to produce a tube of soft rubber with gastric and duodenal ports which has become known as the "Dreiling tube" (15, 16), the mainstay of secretin stimulation tests of pancreatic function for over half a century. However, with the increasingly rare use of this test in recent years, we wonder how many current gastroenterology fellows or recent graduates of gastroenterology training programs would recognize the tube that has become synonymous with the secretin stimulation test—the Dreiling tube. Is it already a relic? Probably. In fact, commercial availability of the tube is now severely limited.

In this issue of the *Journal*, Stevens *et al.* report on a cross-over study of secretin-stimulated endoscopic (ePFT) and Dreiling tube (D-PFT) pancreatic function tests in healthy subjects and demonstrate that the accuracy of the ePFT is comparable to that of the D-PFT (17). With this study, this group adds to their impressive body of work to establish ePFT as an alternative to the previous oroduodenal tube method (8, 18–22). In 2003, they reported their initial results of this relatively new, purely ePFT using synthetic porcine secretin as a replacement for natural porcine secretin which has, at times, been difficult to obtain (18). They were able to demonstrate that this test, which avoided the need for fluoroscopic tube placement and used a standard laboratory autoanalyzer rather than back-titration to measure bicarbonate, was able to distinguish patients with known chronic pancreatitis from those with chronic abdominal pain who were not believed to have chronic pancreatitis. In the same year, they reported their experience with another ePFT involving stimulation with CCK and measurement of lipase in duodenal fluid, again by means of a standard hospital autoanalyzer, and found that this test could distinguish healthy subjects from patients with chronic pancreatitis (19). In subsequent studies using the secretion-stimulation ePFT and autoanalyzer measurement of bicarbonate, they were able to reproduce the anion and cation secretory curves previously observed using oroduodenal tubes and back-titration determination of bicarbonate concentration (21). This later study suggested that the measurement of bicarbonate in timed endoscopic aspirates is comparable to continuous collections via an oroduodenal tube.

As described by this group of investigators and others (23), the test can be performed during routine upper gastrointestinal endoscopy without the need for fluoroscopy. The general features are outlined below [adapted from the investigators' recommendations in conjunction with the ChiRhoClin Website (24)].

1. Subjects are first administered conscious sedation (generally meperidine and midazolam).
2. Esophagogastroduodenoscopy is performed using a standard (10 mm) or thin (6 mm) upper endosocope.
3. A test dose (0.2 μg) of synthetic porcine secretin (*SecreFlo*, ChiRhoClin, Inc., Silver Springs, MD) is given intravenously; and patients are monitored for 1 min for adverse reactions [one patient was reported to have flushing in the initial study (12)].
4. All gastric fluid is aspirated and discarded.
5. Approximately 3–5 cc of fluid should be suctioned from the postbulbar duodenum to rinse residual gastric fluid from the suction channel.
6. At time "0" a baseline collection of 3–5 cc of duodenal fluid is collected in a trap bottle. At time "0" the full intravenous dose of synthetic secretin (0.2 μg/kg, slow push) is administered.
7. Intermittent 3–5 cc fluid aspirates are obtained from the postbulbar duodenum every 15 min for an hour. Each specimen is tightly capped and put immediately on ice.
8. Bicarbonate concentration is determined by a standard hospital autoanalyzer. Fluid should be analyzed within 6 h or may be frozen and analyzed later.
9. The highest bicarbonate concentration from the four samples collected after secretin stimulation (at 15, 30, 45, and 60 min) is considered the peak bicarbonate concentration; a value <80 mEq/L is considered abnormal and indicative of exocrine insufficiency and, in most cases, chronic pancreatitis.

The authors of this latest report have emphasized several practical points (18) including trying to keep the scope tip in the postbulbar duodenum throughout the entire hour-long procedure. When fluid is very sparse, the patient may be put into the supine, reverse-Trendelenburg position to maximize pooling of fluid in the second portion of the duodenum. Low-to-intermediate suction is optimal to minimize mucosal trauma because the presence of blood may effect the bicarbonate concentration.

In our own institution, we have been using the ePFT as performed by Stevens *et al.* (17). We have alerted the clinical chemistry laboratory of the nature of the samples and the likely concentrations of bicarbonate, so that samples can be appropriately diluted. As a check on sample handling and autoanalyzer assay performance, we have asked the laboratory to measure in all samples the concentrations of sodium, potassium, and chloride as well as bicarbonate to assess whether, as expected from physiologic studies of the effects of secretin on pancreatic electrolyte secretion, sodium and potassium concentrations would remain relatively constant as should the sum of the chloride and bicarbonate concentrations (21). On occasion, the deviation from the expected values for these cations and anions has cast doubt on the validity of a given patient's test results, a source of considerable consternation for both patient and physician who are expecting "gold standard" performance from this assay. This raises the question of whether there are some important details involving either specimen handling or autoanalyzer assay methodology which are not obvious from the published methods. Clinicians planning to adopt ePFT should be aware of this and closely evaluate the results they are obtaining.

A very significant unresolved issue concerns the reproducibility of the ePFT sample collection methods and the precision of the bicarbonate determinations. Can a "universal" value for the normal peak bicarbonate concentration (*e.g.*, $\geq$80 mEq/L) be established from the published studies validating this test, or will each center performing this test be required to determine its own normal range by first performing ePFT on an appropriate sample of volunteers who do not have evidence of pancreatic disease? If the latter is the case, this will greatly limit the number of places offering ePFT.

Several criticisms of ePFT have been raised and, in fact, previously discussed by the investigators involved in this current report (22, 25). The need to administer sedation and analgesia may affect pancreatic secretion. The secretin stimulation test employing an oroduodenal tube is performed without sedation. The use of an "ultrathin" endoscope has been reported to obviate the need for sedation (22); although in a practical sense, as the test lasts more than 1 h, this may be difficult for the typical person (let alone a patient with chronic pancreatitis) to tolerate. Prior studies have suggested that pancreatic secretion is affected by narcotics but are not altered by benzodiazepine agents (10, 22, 26). Conwell *et al.* have evaluated the effects of moderate sedation on direct pancreatic function testing and found that dosages of drugs used for conscious sedation in upper gastrointestinal endoscopy have no effect on peak bicarbonate during a 1 h collection period (20).

An additional concern has been the length of time required for performance of the ePFT, slightly more than 1 h. However, this is somewhat shorter than the average time for the traditional oroduodenal tube method ($1\frac{1}{2}$ to 2 h) (22, 25). Attempts have been made to shorten the test, but so far without success. An intraductal secretin test uses three 5-min collections (discarding the first) through a catheter placed into the pancreatic duct at ERCP. However, this collection appears to be too brief for reliable results, and this invasive test carries the risk of acute pancreatitis (27). Perhaps a point in time after secretin administration can be determined at which a single aspiration of duodenal fluid would yield reliable results. However, this awaits further study.

Certain problems will not be completely overcome by the ePFT. Pancreatic juice obtained by duodenal aspiration will still be contaminated by biliary, duodenal, and, to some extent, gastric secretions. However, gastric contamination with ePFT appears to be less of a problem than the potential for Dreiling tube migration into the stomach. False-negative results in some patients with calcific pancreatitis and false-positive results in patients with celiac sprue and malignancies arising from gastrointestinal organs other than the pancreas are still potential problems (1).

Due to the continued contributions of the present group of investigators, direct pancreatic function testing appears to be feasible and practical. They have demonstrated the relative simplicity and reliability of ePFT, bringing it closer to the diagnostic armamentarium of the practicing physician. We may have lost the Dreiling tube but, in its place, gained a "gold standard" which will be more widely used.

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