Vagotomy Plus Bilroth II Gastrectomy for the Prevention of Recurrent Alcohol-induced Pancreatitis

H. HARLAN STONE, M.D., RICHARD J. MULLINS, M.D.,* WILLIAM A. SCOVILL, M.D.

Three retrospective reviews documenting a lessened frequency of acute recurrent alcohol-induced pancreatitis following vagotomy, with or without gastrectomy or gastroenterostomy, prompted a prospective evaluation of truncal vagotomy with Bilroth II gastrectomy as a means of preventing such exacerbations. Randomization between operation and encouragement to abstain from alcohol in patients with a history of more than one, but less than ten, acute bouts of alcohol-induced pancreatitis was set by odd-even digits in the hospital number. Of 176 patients admitted with acute alcoholic pancreatitis during 23 months of study, 49 were excluded because of too few or too many prior attacks. Another 61 refused to enter the study. At least one (average 1.9) recurrence requiring hospitalization was noted in 49, or 80%, of these patients on follow-up for 2 to 26 months (average 14 months). Of the 66 who consented to participate, 33 were randomized not to undergo operation and had almost identical recurrence statistics (*i.e.*, an average of 1.7 recurrences in 24, or 73%). By contrast, only two of 31, or six per cent, allocated to operation have experienced a recurrence ($p < 0.001$). Two who had been randomized were excluded because of persisting active pancreatitis.

AMID ALL THE ARGUMENTS and confusion surrounding pancreatitis associated with alcohol abuse, there is one fact on which all experts agree: the disease tends to recur, almost without exception. Retrospective review of patients admitted with a clinical diagnosis of alcohol-induced pancreatitis revealed that each patient had averated nearly three prior admissions for treatment of a similar acute attack.[1] If the patient had been admitted for the first documented episode of acute alcoholic pancreatitis, chances were greater than 60% that a similar bout would occur within 12 months following discharge. Patients who had experienced two or more attacks of acute alcoholic pancreatitis uniformly had another admission within the ensuing 12 months for treatment of a subsequent episode. Mortality for the first attack of acute alcohol-induced pancreatitis approximated 10%, while subsequent bouts carried a mortality rate of three to four per cent. However, as one recurrence followed another, the cumulative mortalities soon escalated and eventually became quite formidable (*i.e.*, 15 to 25% after five to 10 attacks). In addition, the consequences of chronic pancreatitis, which soon develops and eventually lead to the malnutrition and diabetes of pancreatitis insufficiency, opiate addiction, and loss of the ability to function as a productive member of society must be considered. Accordingly, efforts directed at prevention of this compounding scenario are warranted.

The surgical literature consistently stresses that elimination of alcohol from the diet is of prime importance. Unfortunately, the patient who experiences recurrent bouts of alcohol-induced pancreatitis is seldom receptive to medical advice and rarely, if ever, compliant to directives stipulating abstinence from alcohol. Three retrospective reviews, however, have documented a significant reduction in frequency of recurrent attacks after vagotomy with or without gastrectomy or gastroenterostomy.[2-4] These purported beneficial results prompted the initiation of a prospective, randomized trial of bilateral truncal vagotomy in combination with Bilroth II gastrectomy as a means of preventing future episodes of alcohol-associated pancreatitis in patients deemed to be at high risk for developing recurrent attacks.

Protocol

All patients admitted to the Trauma Service of Grady Memorial Hospital (Atlanta, Georgia) between July 1, 1982 and February 1, 1983, and to the Gastrointestinal Surgical Service of the University of Maryland Hospital (Baltimore, Maryland), between March 1, 1983 and June 30, 1984 with a clinical diagnosis of acute alcohol-induced pancreatitis were considered potential candidates for a study directed at prevention of recurrent attacks. The diagnostic criteria used were classical physical signs

From the Department of Surgery, University of Maryland School of Medicine, Baltimore, Maryland

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* Department of Surgery, University of Louisville School of Medicine, Louisville, Kentucky.

Reprint requests: Dr. H. Harlan Stone, M.D., Department of Surgery, University of Maryland School of Medicine, 22 South Greene Street, Baltimore, MD 21201.

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of acute pancreatitis, significant elevations of serum (>250 units/dl) and/or urinary (>1000 units/dl) amylase, and a history of precipitating heavy alcohol ingestion. Excluded were patients who were younger than 18 years or older than 65 years of age, pregnant or lactating females, presently active pancreatitis and contraindications to operation. In addition, there must have been a history of at least two, but less than 10 prior episodes of acute alcohol-induced pancreatitis, as such categorical patients were presumed to face a high incidence of recurrence without yet having reached a state of chronic pancreatitis.

Those patients who met the criteria were then asked to become subjects for study. The risk of future attacks of pancreatitis, as well as the risk of operation and complications of gastrectomy and vagotomy, were explained. An informed consent thus became the final requisite for inclusion in the study.

Patients were assigned either encouragement to abstain from alcohol alone or vagotomy plus gastrectomy according to the next-to-last digit in the previously assigned hospital number. That digit being odd dictated that a transabdominal bilateral truncal vagotomy, antrectomy, and retrocolic gastroenterostomy (Bilroth II) be performed. An even next-to-last digit specified that enthusiastic encouragement be given to the patient to discontinue the use of alcohol.

Patient demographics, number of previous episodes of alcohol-associated pancreatitis, prior surgical procedures directed specifically at pancreatic disease, concomitant related conditions, and both immediate as well as late operative complications were recorded. Once the patient had been discharged from the hospital, attempts were made to obtain a follow-up visit every 3 months. Failure of the patient to comply was counteracted by mail and telephone surveys. Recurrent suspected attacks of pancreatitis required confirmation using the same criteria as those used for the initial diagnosis.

Results

After 23 months of study, 176 patients had been admitted with a diagnosis of acute alcohol-induced pancreatitis. Of these, 49 were excluded because they had experienced less than two or more than 10 bouts of such. Almost half, specifically 61, refused to become study subjects, thereby leaving 66 patients for randomization. Encouragement to abstain from alcohol was assigned to the 34 with an even next-to-last digit in their hospital number (randomized controls). Vagotomy with Bilroth II gastrectomy was performed on the remaining 32 with an odd next-to-last digit (experimentals). One patient was excluded from each of the randomized study groups; that is, abstinence and operation, because active acute pancreatitis never subsided sufficiently to make either of the patients an operative candidate. For further comparison of results, the 61 patients who originally had refused to participate were similarly followed so as to provide an additional set of controls; these made up a third study group.

TABLE 1. *Documented Prior Attacks of Pancreatitis*

	Refused	Abstain	Vagotomy/Antrectomy
2	16	10	10
3	14	9	12
4	15	7	5
5	7	3	2
6	2	1	—
7	3	—	1
8	2	1	1
9	2	2	—
Total	61	33	31

Patient ages ranged from 19 to 76 years, with an average to 37 years. There were 85 men and 40 women, 118 blacks and seven whites. These 125 patients had experienced 459 separate individual episodes of acute alcohol-induced pancreatitis, thereby making an average 3.7 previous attacks per patient (Table 1).

One or more surgical procedures directed at biliary tract pathology (16), for pseudocyst drainage (12), or involving partial pancreatectomy (4) had been recorded in 27 patients (Table 2). At the time of admission to the study, nine patients were found to have gallstones, five had diabetes mellitus, and seven had presently or recently active peptic ulcer disease. There were no statistically significant differences between the three groups (experimentals, randomized controls, and refusal controls) with respect to any of these basic variables.

Of the 31 patients subjects to operation, prior pancreatitis and its attendant scar created some technical difficulty for vagotomy in two patients and antrectomy in six. Nevertheless, only one immediate complication arose as a direct consequence of the operation itself, this being delayed gastric emptying which persisted until 4 weeks after surgery (Table 3).

There have been no deaths in either the randomized control or experimental group, although two patients in

TABLE 2. *Prior Related Surgical Procedures*

	Refused	Abstain	Vagotomy/ Antrectomy
Patients	61	33	31
Cholecystectomy	5	2	2
Cholecystectomy with common bile duct exploration	2	2	—
Cholecystectomy with sphincteroplasty	2	—	1
Pseudocyst drainage	3	4	5
Partial pancreatic resection	2	1	1

TABLE 3. *Operative Morbidity and Mortality*

Deaths		0
Immediate operative complications		6
Thrombophlebitis	3	
Wound infection	1	
Delayed emptying	1	
Pneumonia	1	
Late operative complications		9
Alcohol gastritis	4	
Early satiety	3	
Dumping	1	
Diarrhea	1	

the control group made up of those who had refused to partipate have died, one of nonpenetrating head trauma, the other from unknown causes. Immediate complications after surgery were minor (Table 3). More significant, however, have been those late problems representing sequelae to gastrectomy and/or vagotomy and more especially severe alcoholic gastritis, such being confirmed by endoscopy following intense alcohol abuse.

No patient who declined study or who underwent operation has given up alcohol. Only three of the patients allocated to enthusiastic encouragement to abstain from alcohol did so.

On follow-up after 2 to 26 months after initiating the study, 49 or 80% of the 61 patients who refused to participate had experienced at least one recurrent episode of acute pancreatitis (Table 4). Similar results were noted for the 33 patients encouraged to give up alcohol, for 24 or 73% had a recurrent bout. In striking contrast was the group of 31 patients who underwent vagotomy with gastrectomy, as only two or six per cent have had another attack of acute alcoholic pancreatitis. Nevertheless, if the patient did abstain from alcohol, acute pancreatitis did not recur. Both the control groups (*i.e.*, patients refusing to enter the study as well as those encouraged to abstain from alcohol abuse) had statistically significant greater rates of acute recurrent pancreatitis ($p < 0.001$), than did the experimental group (*i.e.*, those subjected to the operation).

TABLE 4. *Recurrent Acute Alcohol-associated Pancreatitis**

	Total Patients	Pancreatitis Recurred†	Recurrence per Patient†
Declined participation	61	49 (80%)	1.9 (93)
Encouraged to abstain‡	33	24 (73%)	1.7 (41)
Allocated to operation	31	2 (6%)	1.0 (2)

* Follow-up of 2 to 26 months (average 14 months).

† Recurrences based upon subsequent hospitalization for documented acute alcohol-associated pancreatitis.

‡ Including the three patients who did abstain; none of these three experienced a recurrent episode.

Discussion

Obsession with the premise that a common channel uniformly exists between the common bile duct and the pancreatic duct has dominated surgical thought for almost 80 years.[5] The logical corollary to follow is that such a duct arrangement will routinely lead to the development of pancreatitis whenever obstruction to that confluence occurs. However, there is little evidence to substantiate this presumption of a common anatomic relationship. For example, Mann and Giordano found a true common channel in only 3.5% of patients at autopsy.[6] Out of the 11 instances where pancreatitis were discovered, none had a common channel. Similar absence of an anatomic confluence was reported by Rienhoff and Pickrell, as they could delineate a possible common channel in only 17% of 250 autopsy specimens.[7] Consistently, the anatomic relationships between the main pancreatic duct and the common bile duct are so variable that no absolute norm can be described.[8,9]

Reflux of bile into the pancreatic duct has been shown consistently to cause acute pancreatitis in the experimental animal. Lewis and Wagensteen, in an effort to reproduce the disease in dogs, found that injection pressures of at least 400 mmHg were needed.[10] How such could occur spontaneously in man is open to question, as the highest pressure ever recorded to have been generated in the human was 600 cm H_2O, which is approximately equal to only 60 mmHg.[6] Thus, the minimal reflux pressure necessary to produce pancreatitis in man would be at least 10-fold greater than what can be achieved under physiologic conditions.

Retrograde injection of many substances up into the pancreatic duct can induce acute pancreatitis in the experimental animal. The most effective of all such agents appears to be activated trypsin; its heat-inactivated form is relatively benign.[11] Various combinations of bile, blood, and pancreatic juice, after a period of incubation, have also been used successfully to create the lesion.[12]

A pancreatitis quite similar to what follows the intradural injection of trypsin can be produced by ligation of the pancreatic duct.[13] Reliability of this method and severity of the inflammation is even greater when the gland is actively secreting.[14] Stimulation of the vagus nerve when the pancreatic duct is obstructed results in an acute pancreatitis almost identical to what has been observed when the pancreatic duct is obstructed during the act of secretion.[10] Such has appeared to occur when pancreatic secretions are high in enzyme content rather

than with the so-called pancreatic alkaline tide.[15–17] Similar findings have also been noted following the instillation of peptones and/or hydrochloric acid into the proximal intestinal tract.[18]

The Alcohol Enigma

In patients with a prior history of recurrent bouts of alcohol-associated pancreatitis, the oral ingestion of ethanol often initiates another acute episode and generally aggravates any presently active pancreatic inflammation. Seemingly difficult to explain and in direct contrast is the observation that intravenous administration of ethanol consistently fails to do either.[18]

Stimulation of pancreatic secretion by orally ingested alcohol appears to be through an indirect route. That is, first there is an initial gastric response to the release of endogenous gastrin, which then mediates the secretion of gastric acid, which in turn initiates the release by duodenal mucosa of secretin and pancreozymin, which is finally followed by the active secretion of pancreatic juice.[19] The secretory response to this stimulation by secretion is a pancreatic juice made up primarily of water and bicarbonate.[20] Vagal stimulation of the pancreas, instead, causes the secretion of a protein-rich juice containing the various digestive enzymes.[21] Subsequent destruction of pancreas and peripancreatic tissues as well as the production of various toxic proteins (*i.e.*, vasoactive peptides, etc.) is the direct result of local action by the extravasated pancreatic digestive enzymes, not of any alkaline secretion.

The Vagus Nerve

As stated previously, excitation of the vagus nerve causes the pancreas to secrete a juice rich in digestive enzymes, not in bicarbonate.[21] This response is similar when the pancreas is stimulated by various cholinergic agents.[22] Although truncal vagotomy significantly reduces the pancreatic secretion of both bicarbonate and digestive enzymes in the experimental animal, within a week, water and bicarbonate secretion turns to normal or supranormal levels.[23] The diminished secretion of digestive enzymes, however, remains unchanged.

Serum concentrations of pancreatic digestive enzyme appear to correlate well with intraductal pressure.[24] The extent and severity of any resultant pancreatic acinar damage are not influenced by these same intraductal pressures. Indeed, it is maximal pancreatic stimulation *via* the vagus nerve or by some cholinergic agent alone that consistently produces acinar degenerative changes.[22,24] Vagotomy or anticholinergic drugs, initiated prior to the time of, but not after, a maximal pancreatic stimulation seems to protect the gland against such injury.[14,15,23]

TABLE 5. *Vagotomy to Prevent Recurrent Acute Alcohol-associated Pancreatitis*

	Operation	Patients	Recurred
Richman and Culp	Plus Billroth II	2	0
Pradham et al.	Plus Billroth II	14	3
McCleery et al.	1 With gastroenterostomy 3 Later gastroenterostomies	11	1
Totals		27	4 (15%)

A similar acute pancreatitis can be produced by stimulation of the parasympathetic nervous system through injections of mecholyl.[25] Obstruction of the pancreatic duct increases the reliability of this method for inducing pancreatitis.[14] Parallel increases in pancreatic secretion in humans have followed stimulation with pilocarpine, mecholyl, hypoglycemia, and even psychic excitation.[14,15] Such responses can be blocked by truncal vagotomy.[14,23] Likewise, in a series of animal experiments, vagotomy was found to protect against the development of an acute pancreatitis as would predictively follow obstruction of the pancreatic duct.[13,14]

Three retrospective reviews have documented the efficacy of vagotomy in prevention of recurrent episodes of acute alcoholic pancreatitis (Table 5).[2–4] Richmond and Culp performed vagotomy with Bilroth II gastrectomy on two patients without recurrence, despite a long history in both of repeated bouts of alcoholic pancreatitis.[2] Another group studied 11 patients who had been subjected to vagotomy alone in ten and vagotomy plus gastroenterostomy in an eleventh.[3] Three of the patients later required gastroenterostomy because of gastric outlet obstruction. Ten had no recurrence of pancreatitis, while one subsequently experienced two mild bouts. All patients had a history of repeated episodes of acute alcoholic pancreatitis. In the third study, there were 14 patients who underwent vagotomy with Bilroth II gastrectomy.[4] Eleven had no evidence of recurrence, while three had one recurrence each. Again, all of these patients were known to have a history of repeated bouts of alcohol-associated pancreatitis.

Thus, of the 27 patients subjected to vagotomy, only four had a recurrent episode of pancreatitis (Table 5). In three, only a single recurrence was noted, while in the fourth, the two subsequent attacks were considered to be mild. All patients had been deemed to be at high risk to develop repeated episodes of alcohol-induced pancreatitis in the future. Three other reports have

appeared in the medical literature, but in none have the results been so clearly defined.[26-28]

Acid Secretion

Because good results have been noted when Bilroth II gastrectomy was performed concomitantly with truncal vagotomy, the question naturally arises that possibly true benefit is gained either by extirpation of the antrum or by diversion of acids and/or alcohol away from contact with duodenal mucosa.[2,4] Were this the case, one might anticipate that the administration of cimetidine would provide the needed protection against recurrence if antral activity or hydrochloric acid alone or in combination were all important. However, recent studies have documented the failure of cimetidine to give this desired protection.[29,30] In addition, as previously cited, trypsin release appears to be a crucial component in the evolution of pancreatitis; the acid mechanism for stimulation of the pancreas is *via* contact with duodenal mucosa, followed by elaboration of secretin, ending in secretion of an enzyme-poor, alkaline juice.

In direct contradiction are the beneficial results gained by vagotomy alone.[3] Supporting these clinical observations is the known secretion of enzyme-rich juice whenever the pancreas is stimulated by vagal efferents or by a cholinergic agent. Perhaps an even more appropriate query should then be directed at whether any additional procedure should be added to the vagotomy beyond providing some means to guarantee stomach emptying.

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DISCUSSION

DR. CLAUDE E. WELCH (Boston, Massachusetts): I rise primarily to ask a question. I remember the days when Dr. Ralph Colp, from New York City, proposed Billroth II gastric resection as the primary therapy for pancreatitis of alcoholic nature, because he had never seen a case of pancreatitis after an operation of this type. I think that statement awakened some enthusiasm, but, of course, it was noted shortly after that that there were cases of pancreatitis that did begin after Billroth II resections.

However, enthusiasm persisted. We had a number of patients on whom a combination of operations was done: first, antrectomy plus