References

1. Braasch J. Discussion of reference #6. Am J Surg 1983; 145:492.
2. Cooperman M, Ferrara JJ, Fromkes JJ, Carey LC. Surgical management of pancreas divisum. Am J Surg 1982; 143:107–112.
3. Cotton PB. Duodenoscopic papillotomy at the minor papilla for recurrent dorsal pancreatitis. Endosc Dig 1978; 3:27–28.
4. Cotton PB. Congenital anomaly of pancreas divisum as cause of obstructive pain and pancreatitis. Gut 1980; 21:105–114.
5. Gregg JA. Pancreas divisum: its association with pancreatitis. Am J Surg 1977; 134:539–543.
6. Gregg JA, Monaco AP, McDermott WV. Pancreas divisum: results of surgical intervention. Am J Surg 1983; 145:488–492.
7. Heiss FW, Shea JA. Association of pancreatitis and variant ductal anatomy: dominant drainage of the duct of Santorini. Am J Gastroenterol 1978; 70:158–162.
8. Keith RG, Shapero TF, Saibil FG. Treatment of pancreatitis associated with pancreas divisum by dorsal duct sphincterotomy alone. Can J Surg 1982; 25:622–626.
9. Kruse A. Pancreas divisum: a significantly higher incidence in chronic pancreatitis? (abstr) Scand J Gastroenterol 1977; 12 (suppl 45):52.
10. Mitchell CJ, Lintott DJ, Ruddell WSJ, et al. Clinical relevance of an unfused pancreatic duct system. Gut 1979; 20:1066–1071.
11. Moossa AR. Discussion of reference #2. Am J Surg 1982; 143:111.
12. Richter JM, Schapiro RH, Mulley AG, Warshaw AL. Association of pancreas divisum and pancreatitis, and its treatment by sphincteroplasty of the accessory ampulla. Gastroenterology 1981; 81:1104–1110.
13. Rosch W, Koch H, Schaffner O, Demling L. The clinical significance of the pancreas divisum. Gastrointest Endosc 1976; 22:206–207.
14. Sahel J, Cros RC, Bourry J, Sarles H. Clinico-pathological conditions associated with pancreas divisum. Digestion 1982; 23:1–8.
15. Shapero TF, Keith RG. Pancreatitis and pancreas divisum. Gastroenterology 1982; 83:158 (letter).
16. Traverso LW, Peery WW, Musser G, Frey CF. Pancreas divisum: the role of pancreatic ductal drainage. Surg Gastroenterol 1982; 1:11–16.
17. Tulassay Z, Papp J. New clinical aspects of pancreas divisum. Gastrointest Endosc 1980; 26:143–146.
18. Warshaw AL. Postoperative catheter drainage of the pancreatic duct. Surg Gastroenterol 1983; 2:(in press).
19. Warshaw AL, Cambria RC. False pancreas divisum, an acquired obstruction of the pancreatic duct simulating the congenital anomaly. (Submitted for publication).
20. Warshaw AL, Popp JW Jr, Schapiro RH. Long-term patency, pancreatic function, and pain relief after lateral pancreaticojejunostomy for chronic pancreatitis. Gastroenterology 1980; 79:289–293.

Discussion

Dr. Charles F. Frey (Sacramento, California): Dr. Warshaw, you postulate that the pain in these patients results from a relative imbalance of draining a large portion of the gland through a small duct which has become strictured; yet many of these patients are in their forties and fifties. Why have they not had symptoms earlier? If their pain is due to a late development of a stricture, what is it that is causing the stricture in these patients at this time in their life?

You further postulate, if left untreated, these patients will go on to develop chronic pancreatitis. If this is so, why did one half of your patients in the group with chronic pancreatitis not have an ampullary stricture?

The second question is: Why are your results so outstanding in this group of patients—in fact, better than those reported with any other operation for chronic pancreatitis? Perhaps this group of patients did not have pancreatitis. And the third question is: Pancreatitis is a disease of exacerbations and remissions. How long do you feel these patients should be followed before you conclude treatment is a success?

Dr. William V. McDermott, Jr. (Boston, Massachusetts): This is not a newly-recognized anomaly, certainly. Opie was the first to describe this in 1903, although he is much better known for his famous case of the impacted stone, which he reported with Halsted and which led to the long-standing but eventually moribund concept of the common channel theory of pancreatitis.

Interestingly enough, this did appear in the surgical literature in an article by Dr. Rienhoff in 1945. Other than that, all references to this have been rather abstruse comments from anatomical studies in nonsurgical, nonclinical journals.

The recent resurgence of interest in this anomaly dates from the introduction of endoscopy, when it was possible for the first time to correlate clinical findings—or, at least, attempt to correlate clinical findings with the existence of this anomaly through endoscopic pancreatography. And with the reports of Gregg in this country and Cotton in England in 1977, the floodgates were opened, and, obviously, considerable interest has developed in this presumed syndrome. Dr. Warshaw had a previous report with Richter and his colleagues in 1981 and Dr. Carey of this society also reported, with Cooperman and colleagues, in 1982, on a small operative series.

Last year, we gave reports of our observations on Pancreas Divisum before the New England Surgical Society, and I shall touch briefly on these in this discussion.

As Dr. Warshaw said, the incidence of this anomaly ranges somewhere, by studies available, between 4 and 7%; yet, clearly, there are not that many people walking around with clinical syndromes.

(Slide) The operation we have used in a surgical approach to this problem has not been limited only to the lesser sphincter, but has involved sphincteroplasties of the major and minor papillae, mainly because we were never certain as to what the disease was, and which of the two separate ductal systems it involved.

The total number in our series was 19. (slide) These were selected out of a series of 70 patients who had the association of recurrent epigastric pain and the anomaly of pancreas divisum, and were recommended for surgery because of the severity and intractability of their symptoms. This group comprised mostly women, as seems to have been true in other series; the patients were in the younger age group, the oldest being in the 40s, although the onset of symptoms in all began before the age of 40, at a median age of 26.

I call your attention to the fact that in our series only seven of the cases had any chemical, microscopic, radiological or morphological findings at operation to suggest concurrent pancreatitis, a finding which others have noted as well.

(Slide) The results are somewhat equivocal. Of the 18 patients available for follow-up, one had excellent initial results, although there were four cases in whom some recurrence of symptoms developed in the weeks or months ensuing. This left only 11 patients with good long-term results.

Of the seven patients who had persistent or recurrent problems, further operation were carried out in six, involving a variety of procedures—resection and distal drainage, further papillotomy or 90% resection, with some improvement in 3 cases.

Thus, the results of surgery have not been conclusive to us. I personally have been unable to tell whether this minor sphincter is stenotic, or is just tiny, which it is. It is very difficult to say whether, in the absence of objective findings, there is a definite syndrome of pain associated with relative stenosis, leading to some dilatation of the duct. We have only seen one case of ectasia of the duct, and one other with slight dilatation.

I would leave the audience with this caution and question: Is this a true entity, or chance association? Objective evidence of disease or of clinical pancreatitis associated with the anomaly is sparse.

The other question relates to the fact that abdominal pain, as we all know, is often obscure, or functional in origin, and I wonder still, despite some apparently good long-term results in our series, whether this is an anomaly in search of an operation, or is it actually a disease process?

DR. LLOYD D. MACLEAN (Montreal, Quebec): My colleague, Dr. Larry Stein, in 1000 consecutive ERCPs found 30 cases of pancreas divisum, of which we have operated on very few. But he did go to the autopsy room and did perfusion studies of the pancreatic ducts on routine autopsy patients. (Slide) This is the main pancreatic duct, Wirsung here, Santorini here. He noticed that most of the drainage came out of where you would expect it, at the ampulla of Vater, 2.9 ml/min at 30 cm H_2O head of pressure, in nine cadavers.

When he tied off Santorini, it did not change the flow rate, (slide) and when he tied off Wirsung, it dropped it to zero in 12 cadavers.

(Slide) By chance he did find three cases of pancreas divisum during this study, and then cannulated these ducts separately, with the same head of pressure, and you can see there is much less—about half as much—flow through Santorini as through Wirsung, and this may be the mechanism of the difficulty.

I think I favor what Dr. McDermott has said. I do not think we have seen the proof, although in operating on these patients, one is struck with a gush of pancreatic juice coming out of the duct of Santorini. And when we have operated, this is the operation we have done—*i.e.* on Santorini alone, without touching the ampulla of Vater. I would be interested in knowing what percentage of patients with this problem, with the anatomic defect, you think might actually get pancreatitis.

DR. LAWRENCE W. WAY (San Francisco, California): I would like to congratulate Dr. Warshaw for working so diligently in evaluating these patients, because this is a very timely problem, and it gets into the question of attempting to dissect and find a cause for some of these patients who heretofore have been labeled as having idiopathic pancreatitis. But before we accept everything that we have heard, I would invite Dr. Warshaw to give us some additional information, because as yet I am unclear as to a number of specifics.

First, are we dealing here principally with a pain syndrome, or are these bona fide attacks of pancreatitis? We know, for example, that hyperamylasemia can occur in patients with abdominal pain, and it not always is a true pancreatitis; in fact, some of these patients have elevations of salivary amylase that coincides with the pain, rather than pancreatic amylase. I know Dr. Warshaw has actually contributed some original literature on that subject, and is able to analyze his patients in this regard.

So the question is: What were the amylase levels in these patients? What were the peak levels, and were these patients evaluated for salivary amylase as well as pancreatic amylase?

Patients with episodic abdominal pain, particularly young women, are not a rarity in my practice, having worked in a tertiary care situation for about 15 years now, and one can get frustrated attempting to solve their problems surgically. And, as Dr. Warshaw indicated, we always have some difficulties selecting the patients who have bona fide abnormalities from those whose problems are functional. Surgery has a history of having had operations that seem to have a sound rationale when first proposed, but ultimately did not stand the test of time.

Obviously, a number of these patients have immediate relief of their symptoms, and it has been clear now, as a result of numerous studies of pain and the response of patients to surgery, that surgery has a very profound placebo effect. In fact, it appears from epidemiologic studies of operations now known to have no known sound basis that the placebo effect of surgery generally lasts about 2 years, and then begins to fade.

So I would be interested in knowing, for example, what the length of follow-up is in these patients. How many, for example, had pain relief that lasted for longer than 2 years? Dr. Warshaw listed his good results in terms of how many were followed up for over 6 months.

I think that I would mainly like to have a positive attitude about this, because we certainly need some help in identifying further what the causes are of pancreatitis in patients who do not have a clear-cut explanation.

When patients with idiopathic pancreatitis are followed up for a long period, a large number—perhaps 50% or more—are found ultimately to have some form of gallstone disease. Now, the gallbladders were removed from all these patients. Did you uncover any additional gallstone disease, or even cholesterolosis? Do you know anything about the bile in these patients? Did they have cholesterol crystals? In other words, is it possible to say that this is a group of patients who clearly did not have a subtle form of gallstone disease?

DR. DAVID A. DREILING (New York, New York): Before I could accept obstruction as the pathogenesis of the so-called pancreatitis, I would like to know what the pressures within the pancreatic ducts were. I know it is difficult to cannulate these ducts by endoscopy, but perhaps if you spray the lesser papilla with lidocaine, it will dilate, and enable you to put a catheter in and study the duct pressures under resting conditions and stimulation with secretin. In acute pancreatitis, as the flow decreases, the pressure goes up, and the pressure is the end factor in producing the pancreatitis.

The second question I would like to ask is: In these cases that had so-called acute pancreatitis, do you have any biopsies? It would be extremely interesting to study such biopsies by light and electron microscopy to see whether there is any pathologic lesion. Frankly, I have some skepticism about the pathogenesis and the existence of this syndrome.

My final comment is a question as to whether the pathogenesis might be due to some disease in the Wirsung duct causing it to degenerate. Anatomically, the Wirsung duct in a small percentage of cases does communicate with the duct of Santorini, and if congenitally or by some disease process it becomes obliterated, then the flow must go through the duct of Santorini. Thus, the primary lesion might still conceivably be in the duct of Wirsung.

DR. ANDREW L. WARSHAW (Closing discussion): First of all, the perfusion studies that were shown to us are really fascinating. I had not seen that information before, and I am encouraged to think that it provides some hard data to support what we were looking at from the stenotic other end.

The measurement of pancreatic duct pressure in the live patient is much harder than at autopsy. There are essentially no reported flawless measurements of pancreatic duct pressure in man, except for those in two patients who were cannulated from the tail. All other reported measurements are from cannulas inserted from the duodenum. Any time you put a catheter through the ampulla itself, you are creating at least partial obstruction and obtaining misleading information.

We certainly were concerned about the true diagnosis, nonpancreatic pain vs. pancreatitis. It is frequently a problem to verify the diagnosis of pancreatitis. I quite agree that the patient who has nonspecific abdominal pain is most likely to get a poor result from accessory duct sphincteroplasty. We are emphatically not advocating it for everybody who comes in with belly pain, with or without pancreas divisum. It is no more likely to be a panacea for belly pain than sphincteroplasty of the ampulla of Vater has been. Proper patient selection is paramount.

We are saying that most of the patients that we have selected have had proven pancreatitis, at least as documented by hyperamylasemia and pancreatic edema. At the interval time that we operated on them the pancreas usually looked normal. We do not biopsy it because that would be a dangerous addition to this procedure, and I do not think it is warranted.

We have documented hyperamylasemia in about 80% of our patients. My laboratory performs isoamylase analyses, and I would assure you that this is pancreatic amylase, which originates from no other organ in the body. These patients have had evidence of some kind of pancreatic abnormality, injury, or inflammation during the course of their disease in most cases.

Gallstones have not been responsible for these cases of pancreatitis. In the acute group, 1 out of 32 patients had small gallstones, and because she has not been followed for 6 months, she has not even been included among our good results. The rest had normal or absent gallbladders, with minimal evidence of chronic cholecystitis at most. We do not have bile analyses to tell you whether there were increased cholesterol crystals.

Dr. Frey asked some interesting questions that I will reiterate because I cannot answer them. They are key questions in trying to understand what is going on here.

First of all, if this is a congenital anomaly, why are we seeing it so late in life? Why is the median age as high as, rather than as low as, 28 or 30? I do not know. I do not know whether the stenosis has become more prominent at that phase of life, or whether it is just the long-term accumulation of the effects of a low-grade stenosis. We see some of these patients in childhood and in their teens, and so it may not take all that many years; but still it takes some.

Does pancreas divisum cause chronic pancreatitis? I feel very, very tentative in forwarding that hypothesis. I do not know whether this is a rare and possibly unique example of acute pancreatitis progressing to chronic pancreatitis because of benign pancreatic duct stenosis. That phenomenon is undocumented in any case of biliary pancreatitis. Conversely, I believe that the patient who presents with other kinds of chronic pancreatitis, such as that caused by alcohol, has chronic pancreatitis long before his first symptoms, and that its pathogenesis is not obstructive, at least at the sphincter. Our eight patients had three alcoholics among them. There were stenoses demonstrable in a few of them, but not in most of them, and it may well be that those eight patients represent a coincidence of chronic pancreatitis and pancreas divisum, rather than the much sharper association with stenosis that we saw in the acute group.

Why are the results in eliminating recurrent pancreatitis so good? Why is this the only form of pancreatitis that responds so well to a definitive operation? It is not. In patients with gallstone pancreatitis, removing the gallbladder cures the recurrent pancreatitis. I suggest that if we are lucky enough to detect this disease at an early phase before there is chronic pancreatitis, sphincteroplasty of the stenotic accessory duct orifice removes the lone pathogenetic factor, and, like removing the gallbladder in biliary disease, eliminates the cause of further pancreatitis.

The length of follow-up is certainly important. We are able to say that all patients who were failures, with the exception of two, failed within the first 6 months. The ones who were successes stayed successes after 6 months, with those two exceptions. They had restenosis at 15 months and at 8 months. Both of those have been reoperated upon; both have been followed for a minimum of 8 months since that time, and they have remained asymptomatic.

There are certainly surgical failures, but it does not seem to be simply a question of waiting until the placebo time passes off, at least in most cases. I think we come back again to the question of patient selection, and we do not at the present time have a foolproof means of patient selection. We are hoping that ultrasound examination of pancreatic duct size under conditions of pancreatic stimulation will give us that, where ERCP has not. Time will tell.