Letters to the Editor

What is the Risk of Alcoholic Pancreatitis in Heavy Drinkers?

To the Editor: In Western countries, alcohol abuse is one of the most common causes of acute pancreatitis. However, despite the serious nature of this disease, the risk of pancreatitis in alcohol abusers has never been accurately defined. To determine the incidence of alcohol-induced pancreatitis in a well-defined population, we reviewed records from all patients treated for acute pancreatitis from 1988 to 1995 who resided in the county of Lüneburg (population, ±150,000), in northern Germany. Records were obtained from the regional hospital and from physicians practicing within the region for all patients with a first attack of acute pancreatitis. The diagnosis was based on characteristic signs and symptoms and an abdominal contrast-enhanced computed tomograph obtained within 72 hours of hospitalization.

During the 8-year study period, pancreatitis developed in 220 patients. In 69 patients (61 males, 8 females) alcoholic pancreatitis developed (alcohol consumption ≥60 g/d). The cause was biliary in 90 patients, other causes in 17, and unclear in 44.

Age- and sex-specific prevalence rates for heavy drinkers (≥60 g alcohol/day) were available for 4,759 persons residing in the same region of Germany (1). We applied these prevalence rates to the population of Lüneburg County to obtain an estimate of age-specific frequency of heavy drinkers in our study population.

Table 1 lists age- and sex-specific incidence rates of alcoholic pancreatitis in all persons and in those predicted to be heavy drinkers. For men and women, crude incidence rates for alcoholic pancreatitis in the general population were 10.9 and 1.3/100,000 per year, respectively. Although there were many more male than female patients with alcoholic pancreatitis, among patients at risk (i.e., heavy drinkers), the rate of alcoholic pancreatitis was similar for both sexes (respectively, 91.5 and 81.9/100,000 per year for men and women).

The information in this study came from a single region of one European country. Incidence rates for alcoholic pancreatitis in other countries would be expected to vary, depending on the frequency of heavy drinkers. This study confirms the clinical impression that pancreatitis is an uncommon complication of alcoholism and that there are no differences related to gender. Over a 20- or 30-year period, the risk of developing alcoholic pancreatitis in heavy drinkers is not likely to be more than 2% or 3%. The low frequency of pancreatitis among heavy drinkers implies that other, as yet undetected environmental or genetic factors are important.

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**TABLE 1. Incidence of acute pancreatitis in the general population and in estimated heavy drinkers and alcohol abusers in Lüneburg county (1988–1995)**

<table>
<thead>
<tr>
<th>Age groups (years)</th>
<th>Average population Lüneburg</th>
<th>Incidence cases 1988–1995</th>
<th>Rates per 100,000 inhabitants</th>
<th>Prevalence (%)</th>
<th>Estimated population</th>
<th>Rates per 100,000</th>
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<tbody>
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<td>Men</td>
<td></td>
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<td>0–14</td>
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<td>15–24</td>
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<td>0.00</td>
<td>11.5</td>
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To the Editor: In reply to a letter from Dr. Ulrich Fölsch (Pancreas 2002;24:412–7), Dr. John Neoptolemos discusses seven studies on acute gallstone pancreatitis, including one from our group (1). Because five of the seven studies do not move water to the mill of urgent ERCP, Dr. Neoptolemos claims that those studies are “fundamentally flawed.” With regard to our study, the main flaw would be that our conclusions were drawn from “only 5 patients with bile duct stones and 22 other patients who were found to have stones by stool screening.”

Unfortunately, Dr. Neoptolemos has completely misinterpreted the objective, methods, and results of our study. The objective was to determine the incidence and time course of gallstone migration in patients with acute gallstone pancreatitis and to evaluate the effect of persistent ductal obstruction (more than 48 hours) on the severity of pancreatic inflammation. The method consisted of ultrasound monitoring of sudden diameter changes of biliary and pancreatic duct (2,3). Stool screening was performed only to be sure that ductal diameter changes were secondary to gallstone migration and not the result of ampullary edema or pancreatic swelling. Persistent ductal obstruction was identified in 25 patients, and clinical worsening occurred in only one in whom acute cholangitis developed. Therefore, our study does not support the idea that persistent ductal obstruction promotes pancreatic inflammation. In contrast to Dr. Neoptolemos’ viewpoint, our conclusions were not drawn from 5 patients with bile duct stones and another 22 patients with positive stool screening, but from 25 patients with persistent ductal obstruction secondary to migrating gallstones. Other criticized aspects of our study, such as our “morphological” criteria for patient selection, are debatable opinions that do not deserve to be discussed in this letter.

We agree with Dr. Fölsch that further trials are needed. In fact, a prospective randomized trial on this subject is going on at our hospital. Also, we regret that in the United Kingdom expert referees for the Medical Research Council believe that there is “no longer any case to answer.” It is our belief that there is still much to be learned from patients with acute gallstone pancreatitis.

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REFERENCES

Role of Urgent Endoscopic Sphincterotomy in Severe Gallstone Acute Pancreatitis: Reply to Professor Alejandro Oria

To the Editor: I am pleased to reply to the comments relating to the debate on the role of urgent endoscopic sphincterotomy in severe gallstone acute pancreatitis (Pancreas 2001;22:221–9 and Pancreas 2002;24:412–8) raised by Professor Alejandro Oria. Of course if this role were clear then there would be no debate. If then we choose to enter into the debate, we should seek to illuminate the evidence that exists. It is not a question of the number of studies in support of any particular concept versus the number of studies against. One good randomized study that tests a clinical hypothesis is worth countless “personal experiences” or any number of poorly designed and/or underpowered trials.

Professor Alejandro Oria contests my view (Pancreas 2002;24:412–8) that his study of bile duct stones in acute pancreatitis (1) can tell us nothing about the pathogenesis of severe gallstone pancreatitis. To gain adequate data on this question, we require a large number of patients with the following:

(a) acute pancreatitis;
(b) gallstones;
(c) bile duct stones;
(d) adequate imaging;
(e) severe and mild acute pancreatitis

Our conclusions based on our own studies (2–12) can be summarized as follows.

(i) Bile duct stones are more likely to “persist” in the bile duct in severe acute pancreatitis (61% at <72 hours and 50% at 3–30 days post onset) compared with mild pancreatitis (35% at <72 hours and 24% at 3–30 days after onset). This evidence is based on a study of 100 patients (38 with severe disease) undergoing emergency ERCP during the acute phase of the attack (6). Severity was assessed prospectively using accepted and properly applied Glasgow (modified Ranson) criteria. Fifty-five patients had ERCP within 72 hours of admission including 26 severe cases—and we know that in the UK the median time to hospital admission is 7 hours compared with, for example, Germany, where this is 24 hours (12).

(ii) Stones that initiate the attack of acute pancreatitis need to be separated from “persisting” stones that contribute to the subsequent severity of the attack (8).
(iii) Necrotizing pancreatitis evolves over days or weeks and is not entirely “pre-determined” on day one of the illness (9,10).
(iv) Gallstones may “persist” in the bile duct because (a) the stone that caused the attack has passed, and more stones have passed into the bile duct from the gallbladder; (b) the stone that initiated the attack has refluxed back into the main bile duct after having temporarily lodged in the ampulla of Vater; and (c) has remained impacted in the ampulla of Vater (8).
(v) Patients with a severe attack tend to have (a) a larger bile duct diameter than those with a mild attack; (b) an increased main pancreatic duct; (c) biochemically elevated bilirubin; and (d) significant correlations of the aforementioned with each other. Elevated serum liver transaminases within 48 hours of an attack are associated with gallstones in acute pancreatitis but neither with “persisting” bile duct stones nor with clinical severity (2,3,5,6,11).
(vi) Acute cholangitis is significantly more frequently associated with severe acute pancreatitis than with mild pancreatitis. Urgent endoscopic sphincterotomy improves outcome both from acute cholangitis and acute pancreatitis (4,7).
(vii) Urgent endoscopic sphincterotomy is associated with improved outcome in severe acute pancreatitis and does not increase morbidity in mild acute pancreatitis (7).

So against this background let us examine the study by Professor Alejandro Oria and his colleagues.

(a) A diagnosis of gallstone acute pancreatitis was based on a serum amylase at least twice the upper limit of normal. This is too loose a benchmark, as this will include many patients with gallstones but without acute pancreatitis. The preferred cut-off level for amylase is five times the upper limit of normal and certainly not less than three. Moreover, the amylase levels are much higher in gallstone associated acute pancreatitis compared with other causes, so there is no need to have such a low diagnostic threshold that would undermine a scientific study (2). They diagnosed 110 patients in this manner but kept only the 51 patients that they said had acute pancreatitis identified at operation sometime later (in fact at least two patients had post-mortem without surgery!). Since all but one of the remaining patients underwent surgery at least 2 weeks after admission (no median time or dispersion values were given), we do not know how many cases actually had mild pancreatitis that resolved.

(b) Detection of bile duct stones by abdominal ultrasound has a very low sensitivity in acute pancreatitis, especially in the acute phase and in a severe attack (2,3). A technique that has, for example, a 50% error rate is hardly of relevance to a scientific study. That is why we used ERCP so extensively (and not ultrasonography) to obtain accurate figures on the presence or absence of bile duct stones. Unfortunately, in the final analysis, the study of Professor Alejandro Oria and colleagues only identified five patients with bile duct stones.

(c) The finding of stones in the stool of 22 other patients is not relevant to the debate, as this does not differentiate between initiating stones and “persisting” stones. According to Acosta and Ledesma (13), the figure should actually be nearer to 100% (compared to 10% for patients with biliary colic but no acute pancreatitis). The presence of stones in the stool does not tell us (i) if they had acute pancreatitis or just biliary colic; (ii) if they were “persisting” stones or not; and (iii) whether an attack of acute pancreatitis was mild or severe. In other words, having this information is pointless.

(d) The number of patients with severe acute pancreatitis is obscure. We know from the clinical outcome that there were five severe cases. It is suggested, however, that there were cases with high Balthazar CT severity index scores (presumably in addition to the two early deaths) and cases with high Ranson scores (presumably including the two early deaths). Unfortunately Professor Alejandro Oria has little idea regarding the application of either to the objective scoring of severe acute pancreatitis. Balthazar CT severity index score: 19 patients were identified with two or more points, but this score is too low to be of value. For comparison, the median Balthazar severity index score in our last 54 patients with severe acute pancreatitis undergoing surgery was 8.5 of a maximum of 10. Ranson score: 19 patients were identified with two or more points. Unfortunately, patients with two points cannot be classed as severe. They measured the “Ranson” score on admission and every 3 days thereafter. Unfortunately, the Ranson score only has diagnostic accuracy at 48 hours, not before and not afterwards! Thus the information on the Balthazar and Ranson scores is relatively pointless except that it points to perhaps all but five patients with mild disease.

Professor Alejandro Oria et al. concluded that bile duct stones were not related to severity. Such a conclusion is impossible based on only five cases with bile duct stones and only five cases with severe acute pancreatitis. Unfortunately they did not have sufficient data to support any conclusion.

Finally it is worth summarizing the published trials as follows.

1. The study by Stone et al. (14) contained mostly patients with mild disease and was underpowered.
2. The study by Kelly and Wagner (15) involved prior knowledge of the randomization and inappropriately applied the Ranson score (with probably more severe cases in the urgent surgery arm). In addition, the surgery performed did not involve cutting the sphincter of Oddi. (How placing a T-tube into the bile duct is meant to improve acute pancreatitis has never been explained to me).
3. The results of our study (7) showed reduced morbidity in the treatment arm.
4. The study by Fan et al (16) showed identical results to ours once the 35% of patients without gallstones were excluded, despite the fact that nearly one third of the
conservative group also had sphincterotomy (and mostly <72 hours).

5. Finally, interpretation of the study by Fölsch et al (17) remains obscure because the authors have refused to answer vital questions about the trial (Pancreas 2002;24:412–8). These include the following.

- How can one apply severity stratification post hoc when the intervention to be tested precedes this?
- How does one explain a mortality of 23% in the ERCP severe group when in the Leicester and Hong Kong trials this was <4.0%?
- How does one explain a mortality of 8% in patients without severe disease in the ERCP group when it is 0% in other studies?
- How is it possible for there to be more cases developing acute cholangitis in the sphincterotomy group than in the conservative arm (especially when presenting acute cholangitis was a specific exclusion criterion)?
- How many patients died after sphincterotomy, and how many died who did not have a sphincterotomy? These are extremely important questions, and refusal to answer them surely totally undermines the interpretation of the trial.

Both Professor Uli Fölsch and I have proposed to work together in a joint trial to obtain more data. Unfortunately this has not proved to be possible for various reasons beyond our control. We look forward to seeing the results of the trial currently being undertaken by Professor Alejandro Oria. In the meantime, it is important to base clinical practice on the most objective interpretation of the data available. I believe that Professor Uli Fölsch and I have been able to clarify some of the confusion—although not as much as everybody would wish for.

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REFERENCES


Acinar Cell Carcinoma of the Pancreas in a Morbidly Obese Patient

To The Editor: In reviewing the literature, we find that the development of pancreatic cancer due to obesity is difficult to establish and controversial due to the fact that more than one risk factor for the development of pancreatic cancer may co-exist in the obese patient, such as alcohol intake or tobacco smoking (1). We recently treated a patient who was morbidly obese and was found to have acinar cell carcinoma of the pancreas at autopsy. We find this case interesting not only due to the rare malignancy this young patient had but also for the usual presentation and postoperative course following Roux-en-Y gastric bypass for the treatment of morbid obesity.

The patient was a 44-year-old white male who had a history of morbid obesity. He weighed 100 kg at the time of graduation from high school and gained weight progressively despite numerous diet, exercise, and behavior modification programs. He had been previously evaluated for surgical intervention, but his weight placed him at too high a risk for a bariatric procedure. Thus, he was advised to lose weight medically before proceeding with surgical intervention. Unfortunately, his obesity only worsened, making him bedridden with shortness of breath on minimal exertion. Therefore, surgical intervention was the last resort and he was admitted to the hospital for a gastric bypass operation. At the time of admission, his body mass index (BMI) was 119 kg/m².

The patient’s medical history was significant for obstructive sleep apnea, chronic obstructive pulmonary disease, and lower back pain. He had been a heavy smoker and quit 3 months prior to this admission. He had not been taking any medications and had no known allergies. His family history was significant for a cousin who was morbidly obese. There was no family history of malignancy.

On physical examination, the patient had normal vital signs and was in no acute distress. His heart had a regular rate and rhythm. His lungs revealed crackles throughout. His abdomen showed extreme obesity without tenderness or...
scars, and he had extensive erythematous nodules in the lower abdomen, consistent with panniculitis. His extremities were edematous with varicose veins.

The patient was hospitalized for medical optimization in preparation for a gastric bypass. He had severe pulmonary hypertension with pulmonary pressures of 94/48 mm Hg. He was started on aggressive diuresis with intravenous torsemide, to the point that he was losing approximately 15 L a day for more than a week. By the time of surgical intervention, he had lost 160 lb by diuresis alone. His pulmonary pressures did not improve, however, and therapy with intravenous heparin was empirically started with a presumptive diagnosis of chronic pulmonary emboli. Antibiotic treatment was started for suspected infected abdominal panniculitis.

He underwent surgical intervention 13 days after his admission. The original plan was to perform a staged operation with a jejunoileal bypass (JIB) first, followed by a Roux-en-Y gastric bypass after weight loss. This would eliminate the risk of exploring the upper abdomen. Surprisingly, he had favorable anatomy and underwent a routine Roux-en-Y gastric bypass. There were no complications intraoperatively. However, his postoperative course was immediately complicated by respiratory failure, and a few days postoperatively he required a tracheostomy due to the inability to be weaned off ventilatory support. His pulmonary pressure remained elevated throughout the hospitalization. He subsequently developed renal insufficiency requiring dialysis.

The positivity of bacterial cultures of urine, wound, and central venous catheter specimens was reported 1 week after the operation. He was placed on a “do not resuscitate” status and became asystolic 12 days after the operation.

An autopsy was performed the following day. The cause of death was cardiopulmonary failure that was probably caused by his severe pulmonary hypertension. Pathological examination of his pancreas revealed a tumor with marked cellularity with cells positive for periodic acid–Schiff diastase digestion (d-PAS) in the cytoplasm, consistent pancreatic acinar cell carcinoma. Further examination revealed metastasis to hilar lymph nodes.

The present case is unusual because the patient did not have the history expected with a pancreatic malignancy. Acinar cell carcinoma of the pancreas by itself is a rare malignancy, accounting for less than 2% of all exocrine tumors (2). Weight loss rather than obesity is expected in patients with acinar cell carcinoma of the pancreas. It is unclear, however, whether obesity was a contributing risk factor, as he had a history of smoking, making the association less obvious.

Another unusual feature of this case was that this patient presented with panniculitis. Pancreatic panniculitis is often seen in pancreatic cancer due to increased secretion of lipase, amylase, or trypsin by the cancerous cells (2). However, in the present report this patient had normal serum lipase and amylase levels. Additionally, because fat necrosis is commonly seen in obese patients due to increased adiposity (3), whether his panniculitis was due to his malignancy, his obesity, or both is unclear.

The most perplexing aspect of this case was the patient’s uncontrolled pulmonary hypertension. Acinar cell carcinoma of the pancreas is characterized by the release of various pancreatic enzymes, which can serve as diagnostic markers for this disease (4). Most series report trypsin as the most common pancreatic enzyme secreted by these tumors. However, several other enzymes have been reported (5). Although pulmonary hypertension commonly occurs in the obese patient as a result of long-standing obstructive sleep apnea, it typically responds well to medical management. In the present case, however, the patient’s pulmonary hypertension could not be controlled even with aggressive diuresis or intravenous heparin therapy. Additionally, there was no evidence of pulmonary pathology at autopsy that could explain the observed pulmonary hypertension. A comprehensive review of the literature did not yield an association between acinar cell carcinoma of the pancreas and pulmonary hypertension. Whether there is in fact an association between these two diseases in not known.

There are several possible associations in this case. As the numbers of bariatric operations continue to increase in the United States, these associations may become more evident, which will perhaps indicate a stronger link between obesity and carcinogenesis. Thus far, to our knowledge this is the first report of a morbidly obese patient with occult pancreatic cancer.

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REFERENCES

Do Mast Cells Play Any Role in the Pathogenesis of Experimental Pancreatic Fibrosis in Rats?

To the Editor: We recently reported the role of mast cells in closed duodenal loop (CDL)–induced pancreatitis using mast cell-deficient Ws/Ws (white spotting of the skin) rats (1). Ws/Ws rats have a 12-base deletion in the tyrosine kinase domain of the c-kit gene and are genetically deficient...
in both connective tissue-type and mucosal-type mast cells (2). In this study, we found that pancreatic mast cells do not play a crucial role in this short duration model. We speculated that the number of mast cells in the pancreas is not enough to contribute to the pathogenesis of that model of pancreatitis in both Ws/Ws and control rats. Thus, we wondered whether mastocytosis in the pancreas, which can be induced by some stimuli, influences the pancreatic pathology.

Recently, an experimental pancreatic fibrosis model was reported by Matsumura (3). In this model, pancreatic fibrosis is induced by the intraperitoneal injection of a superoxide dismutase inhibitor, diethyldithiocarbamate (DDC), twice a week for at least 2 weeks. DDC induced accumulation of reactive oxygen species (ROS) in the pancreas (3). The effects of this inhibitor strongly suggest a relationship between fibrosis and tissue oxidative stress. On the other hand, a relationship between tissue mast cells and tissue fibrosis has been suggested in some organs. Therefore, we have investigated whether this model induces mastocytosis in the pancreas and the roles of mast cells in this pancreatic fibrosis model, and herein we report some interesting results.

TABLE 1. Histologic damage scores, mast cell counts, and hydroxyproline contents of DDC-induced pancreatic fibrosis in the Ws/Ws and control (+/+) rats

|                     | Untreated Ws/Ws | DDC-treated Ws/Ws | Untreated control (+/+) | DDC-treated control (+/+)
|---------------------|-----------------|-------------------|--------------------------|--------------------------
| Inflammation        | 0.6 ± 0.2       | 1.4 ± 0.2         |                          |                          |
| Fat replacement     | 0.6 ± 0.3       | 2.6 ± 0.3         |                          |                          |
| Total               | 1.2 ± 0.2       | 4.0 ± 0.5         |                          |                          |
| Mast cell counts (count/mm²) | 0.01 ± 0.01     | 5.18 ± 1.02       | 1.54 ± 0.40              | 10.10 ± 1.00             |
| Hydroxyproline (mmol/g wet weight) | 3.80 ± 0.08    | 6.20 ± 0.51       | 3.80 ± 0.08              | 4.20 ± 0.15              |

Values are mean ± SEM.  
* p < 0.05.  
** p < 0.05 vs. untreated Ws/Ws.  
*** p < 0.05 vs. untreated control (+/+).  
**** p < 0.05 vs. untreated blank and DDC-treated control (+/+). by Mann-Whitney U test.

WS/Ws and normal control (+/+) rats were obtained from SLC, Inc. (Shizuoka, Japan). The rats received intraperitoneal injections of DDC (500 mg/kg) twice a week for 2 weeks (n = 5) (3). In this study, two rats in each group were untreated.

After 2 weeks, the entire pancreas was removed, and its wet weight was measured.

Sections from the pancreas were removed, fixed in Carnoy’s fixative, and stained with hematoxylin and eosin (HE). The tissue damage was scored according to a previously described method with modifications (3,4). The following two parameters were used. Inflammatory cell infiltration was scored as 0, absent; 1, mild (<50% of parenchyma); and 2, moderate (>50% of parenchyma). Acinar fat replacement or atrophy was scored as 0, absent; 1, mild (≤5% of parenchyma); 2, moderate (5–20% of parenchyma); and 3, severe (20–50% of parenchyma). The sum of the two scores was defined as the mucosal damage score for each animal. In addition, toluidine blue staining (pH, 2.5) and elastica van Gieson staining were also performed to evaluate the number of mast cells and the amount of collagen in the pancreatic parenchyma, respectively. Tissue col-

FIG. 1. Microscopic findings and relationship between hydroxyproline content levels and mast cell counts in diethylidithiocarbamate (DDC)-induced pancreatic fibrosis in Ws/Ws and control (+/+) rats. A: DDC-treated Ws/Ws rat and (B) control (+/+) rat pancreas in toluidine blue staining (original magnification ×200). Arrows indicate the tissue mast cells and their degranulation. (C) DDC-treated Ws/Ws rat and (D) control (+/+) rat pancreas in elastica van Gieson staining (original magnification ×100). E: Relationship between hydroxyproline content levels and mast cell counts in the pancreatic parenchyma. The line represents the regression line for data from both DDC-treated Ws/Ws and control (+/+).
The histologic damage is summarized in Table 1. Both inflammatory cell infiltration and acinar fat replacement or atrophy were significantly higher in the DDC-treated control (+/+)
rats than in the DDC-treated Ws/Ws (+/+)
rats.

DDC treatments increased the mast cell counts in the pancreatic parenchyma in both the Ws/Ws and control (+/+)
rats (Fig. 1A and B), as revealed by toluidine blue staining. The mast cell counts per mm² in these four groups are summarized in Table 1. The mast cell counts increased in the following order: DDC-treated control (+/+)
> DDC-treated Ws/Ws > untreated control (+/+)
> untreated Ws/Ws

DDC treatment increased the amount of red-stained collagen in the pancreatic parenchyma in the Ws/Ws and control (+/+)
rats (Fig. 1C and D, in which fibrosis is evidenced by dark elastica van Gieson staining).

The hydroxyproline content of the pancreatic parenchyma in the four groups is summarized in Table 1. DDC treatment increased the collagen content in the pancreatic parenchyma in both the Ws/Ws and control (+/+)
rats. The collagen content in the DDC-treated Ws/Ws rats, however, was significantly greater than in the DDC-treated control (+/+)
rats. In addition, a strong negative correlation was observed between hydroxyproline content and mast cell counts in the pancreas (Fig. 1E).

In general, mast cells have been reported to be closely associated with the development of tissue edema and hyperemia. Potent chemical mediators such as histamine, leukotrienes, and platelet activating factor (PAF), which are released by the mast cells, play an important role in this process. However, it is unclear whether mast cells could contribute to tissue fibrosis. Okazaki reported that the magnitude of pig serum–induced liver fibrosis and bleomycin-induced lung fibrosis were more severe in the Ws/Ws rats than in the control (+/+)
rats (6). Zheng reported that mast cells protected the intestine from mucosal injury during the early phase of radiation injury and promoted intestinal fibrosis during the delayed phase in Ws/Ws rats (7). In studies using conventional rats, it was suggested that mast cells promote fibroblast-dependent fibrosis in the experimental model of tetrachloride-induced cirrhotic liver (8).

The current study yielded four important findings. (1) DDC induced pancreatic fibrosis for a short period (2
weeks). (2) DDC induced mastocytosis in the control (+/+)
rats and the recruitment of mast cells in the Ws/Ws rats. Stimuli of long duration, such as certain parasite infections and dextran sulfate sodium–induced colitis, have been shown to induce the recruitment of mast cells in Ws/Ws rats (9,10). (3) Tissue mast cells probably contributed to the inhibition of DDC-induced pancreatic fibrosis; pancreatic fibrosis was gradually inhibited in accordance with increased mast cell counts.

(4) Conversely, acinar fat replacement or atrophy and inflammatory cell infiltration in the pancreatic parenchyma were reduced in the DDC-treated Ws/Ws rats as compared with the DDC-treated control (+/+)
rats, similar to observations in other organs (9).

Collectively, these results indicate that mast cells might contribute to tissue damage and fibrosis. Whether the mast cells recruited by DDC function normally and whether the disturbed c-kit gene influences pancreatic function involving fibroblasts, however, remain to be investigated. In addition, the interactions between pancreatic mast cells and ROS are still unclear. However, a strongly negative correlation between collagen content and mast cell counts in the pancreatic parenchyma strongly suggests that mast cells may have an important role in the inhibition of fibrosis, although it is still unclear whether this effect is exerted through collagenolysis or collagenogenesis.

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