Virchows Archiv A Pathol Anat (1992) 420:1–4

Virchows Archiv A
Pathological Anatomy and Histopathology

Hypothesis

The morphological basis for the evolution of acute pancreatitis into chronic pancreatitis

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Received September 3. 1991 / Accepted September 26, 1991

The pathogenesis of chronic pancreatitis is still unsettled. The most commonly cited theory postulates the deposition of protein plugs which later calcify, leading to duct obstruction with subsequent fibrotic replacement of the acinar tissue upstream of the occlusion (Sarles 1986). We proposed an alternative working hypothesis that relates the pathogenesis of chronic pancreatitis to that of acute pancreatitis (Klöppel 1990; Klöppel and Maillet 1991). The sequence of events that we believe may connect acute with chronic pancreatitis starts with interstitial fat necrosis and haemorrhage, inducing perilobular fibrosis. Perilobular fibrosis, in turn, may also distort the interlobular ducts, creating stenoses and dilatations. The ducts, once altered, hamper the normal flow of pancreatic secretions, thereby enabling the precipitation of proteins (protein plugs) and eventually their calcification (calculi). If duct obstruction becomes more extensive, the acinar cells upstream of such a stenosis will disappear, leaving dense intralobular fibrosis. This chain of events has been provisionally termed the necrosis-fibrosis sequence (Fig. 1). If this necrosis-fibrosis sequence is indeed the basic pathogenetic principle underlying chronic pancreatitis, it must also be consistent with a number of observations that seemingly contradict it. In this contribution special emphasis has been placed on answering the following questions: (*1*) Why has pancreatic fibrosis characterizing chronic pancreatitis typically a patchy pattern, although acute pancreatitis is thought to be a diffuse disease; (*2*) Why does biliary pancreatitis virtually never progresses to chronic pancreatitis (Dürr 1979; Gullo et al. 1984); (*3*) Why does every relapsing alcoholic pancreatitis not progress to chronic pancreatitis; and (*4*) When does chronic pancreatitis progress?

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Why is chronic pancreatitis a focal disease?

There is general agreement that the fibrotic process characterizing chronic pancreatitis affects the pancreas unevenly (Uys et al. 1973; Gyr et al. 1984; Klöppel and Maillet 1991). In a typical case, areas with some perilobular fibrosis, or even normal acinar parenchyma, alternate with severe perilobular and intralobular fibrosis. If such a patchy pattern of fibrosis is to be due to a necrotic process, this process must be focal as well. Yet, acute pancreatitis is thought to be a diffuse disease, implying that all parts of the pancreas are evenly affected. This concept, however, is not consistent with the distri-

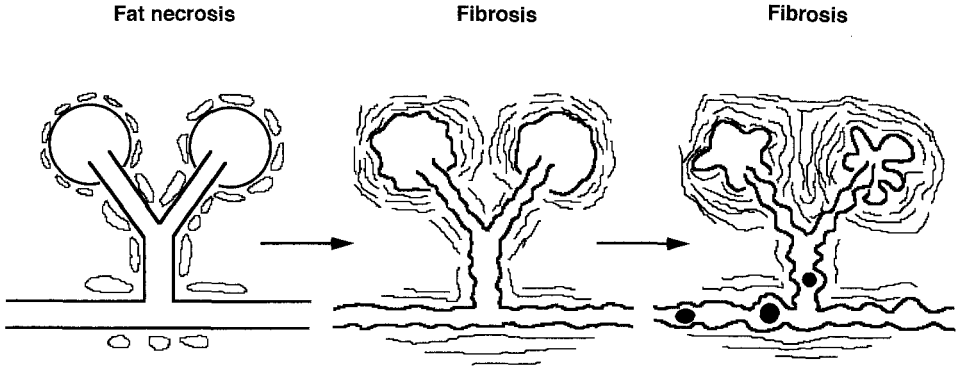

Fig. 1. The "necrosis-fibrosis sequence" schematically summarizes the main events and findings that connect acute with chronic pancreatitis. *Left:* Pancreatic lobule and duct surrounded by interstitial fat necroses. *Centre*: Pancreatic lobule encased by fibrosis that also involves the draining interlobular duct. *Right*: Pancreatic lobule partly replaced by intralobular fibrosis and encased by advanced perilobular fibrosis. The distorted draining duct is obstructed by calculi

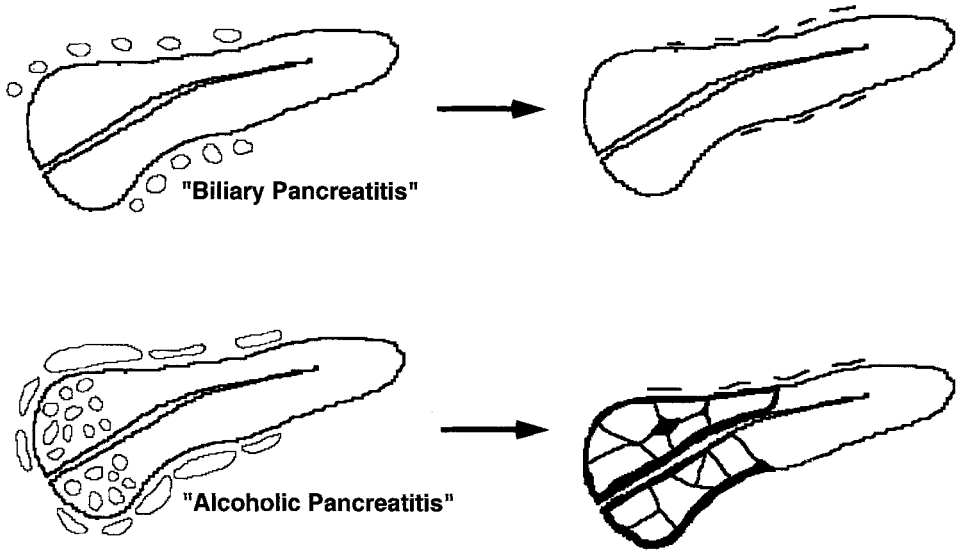

Fig. 2. Natural history of acute pancreatitis. *Upper panel*: Acute pancreatitis that is characterized by peripancreatic fatty tissue necrosis (mild or severe) and clinically often corresponds to biliary pancreatitis, does not proceed to chronic pancreatitis. *Lower panel*: Acute pancreatitis that is characterized by peripancreatic and intrapancreatic necroses and clinically often corresponds to alcoholic pancreatitis may go on to chronic pancreatitis

bution pattern of necrosis that one usually finds in severe acute pancreatitis. Although the surface of pancreatic specimens with severe acute pancreatitis shows confluent fat necrosis and haemorrhage suggesting diffuse involvement of the organ, analysis of the parenchyma of the gland reveals, as a rule, that it is well-preserved in many parts and displays only foci of haemorrhage and interstitial fat necrosis (Schmitz-Moormann 1981; Klöppel et al. 1986). These focal changes may be confined to only one area of the pancreas (the head or tail), leaving the other parts of the gland completely unaffected. It is unclear which mechanisms govern the distribution of the necrotic lesions within the pancreas, because the damage patterns differ from patient to patient and do not follow any recognizable rule.

From these findings it is evident that acute pancreatitis is, morphologically speaking, not a diffuse disease, but a focal process, the pattern of which compares well with the irregularity of fibrosis seen in chronic pancreatitis. We therefore believe that the primarily focal nature of chronic pancreatitis reflects the intrapancreatic damage pattern observed in severe acute pancreatitis.

Why does biliary pancreatitis seldom progress to chronic pancreatitis?

According to clinical studies it appears that gallstone pancreatitis, even if relapsing, rarely (or virtually never) progresses to chronic pancreatitis (Dürr 1979; Gullo et al. 1984). This observation seems to contradict our necrosis-fibrosis hypothesis of pathogenesis, since it implies that there is a large group of patients whose acute pancreatitis is never followed by pancreatic fibrosis. To explain this finding, it has to be taken into account that biliary pancreatitis is usually a mild (also called interstitial-oedematous) acute pancreatitis. The morphology of mild acute pancreatitis is characterized by some spotty peripancreatic fat necroses that barely involve the gland (Gyr et al. 1984; Klöppel et al. 1984). Accordingly, these peripancreatic lesions resolve without any influence on the architecture of the pancreatic parenchyma, and even if the same lesions recur, the glandular tissue remains intact (Fig. 2). It can thus be concluded that mild acute pancreatitis never produces intrapancreatic changes such as perilobular or periductal fibrosis. Biliary pancreatitis is therefore not likely to evolve into chronic pancreatitis.

Why does not every relapsing alcoholic pancreatitis progress to chronic pancreatitis? When does chronic pancreatitis progress?

It has been shown that some patients with relapsing alcoholic pancreatitis do not progress to chronic pancreatitis clinically (Ammann et al. 1986). Conversely, it is also well known that the morphological substrate of relapsing alcoholic pancreatitis is usually chronic pancreatitis with the tendency for self-perpetuation (Comfort et al. 1946; Nagata et al. 1981; Ammann et al. 1984). To explain these observations and to get an idea about a patient's risk of developing a progressive chronic pancreatitis, the possible extent of damage in severe acute pancreatitis, its localization in and around the pancreas, and its consequences to the pancreatic duct system have to be considered (Fig. 2).

In many patients, severe acute pancreatitis leads to massive peripancreatic fat necrosis predominantly over the surface of the pancreas, while the intrapancreatic regions are virtually unaffected. The massive peripancreatic necrosis is transformed into extrapancreatic pseudocysts that may cause complications but do not lead to significant intrapancreatic fibrosis with duct alterations (Fig. 3). Consequently, this type of severe acute pancreatitis will not progress to chronic pancreatitis.

In other patients with severe acute pancreatitis, peripancreatic necrosis is associated with some small foci of intrapancreatic necrosis. The sequelae of these lesions are extrapancreatic pseudocysts and small foci of scarring within the pancreas. If the intrapancreatic fibrotic

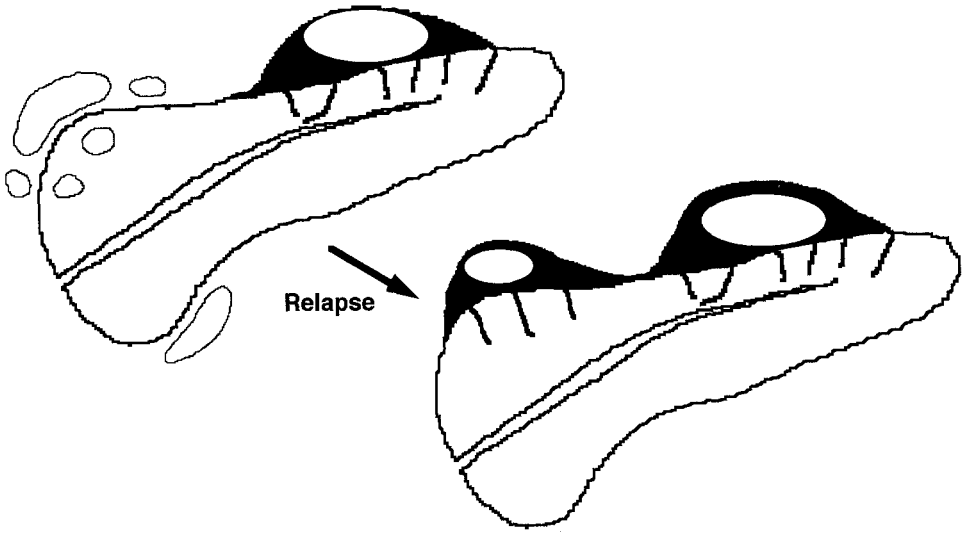

Fig. 3. Natural history of relapsing severe acute pancreatitis with necroses mainly restricted to the peripancreatic fatty tissue and the peripheral pancreatic parenchyma. The postnecrotic sequellae, i.e. pseudocyst and peripheral scarring, do not go on to progressive chronic pancreatitis

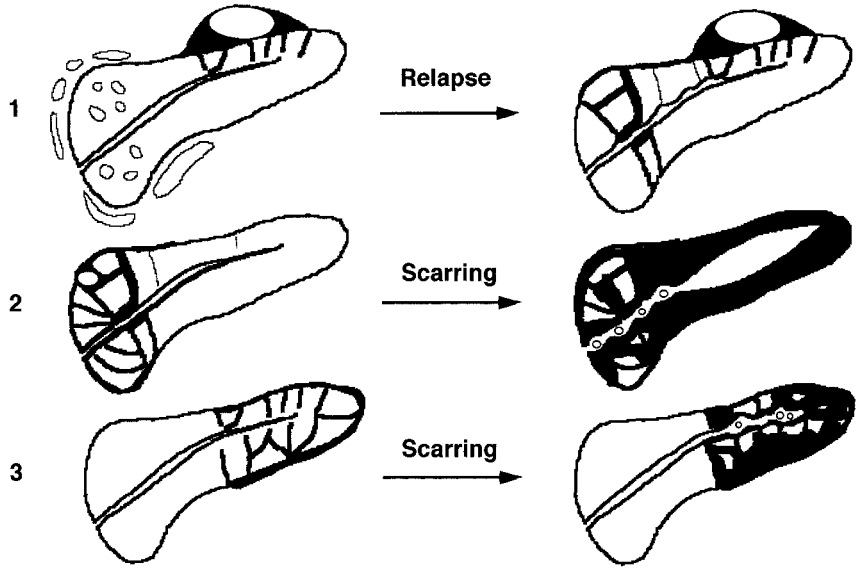

Fig. 4. Natural history of progressive chronic pancreatitis. The first type is characterized by acute relapses that involve the peripancreatic tissue as well as the pancreatic parenchyma, including the duct system. The second type is characterized by chronic damage to the pancreatic head which subsequently induces progressive obstructive changes in the body and tail of the pancreas. The third type is characterized by damage to the body/tail that in time will locally progress but remain restricted to this area

foci do not involve the main pancreatic duct and its direct branches, progression of the disease is unlikely to occur. It will, however, progress, when the patient continues to abuse alcohol so that further attacks of pancreatitis can occur. These now affect regions adjacent to the main pancreatic duct, resulting in alterations of the branches and eventually of the main duct (Fig. 4).

The third group of patients shows severe acute pancreatitis with marked extrapancreatic fat necrosis as well as large foci of intrapancreatic necrosis (Fig. 4). This pancreatitis, particularly if relapsing, causes not only pseudocysts but also pancreatic fibrosis that already initially involves the main duct in the affected areas and leads to its distortion. In these patients, progression to chronic pancreatitis is most likely, even after alcohol abstinence. The clincal severity of the resulting chronic pancreatitis then depends on whether the damage was mainly to the head of the pancreas or to the body and/or tail. When the head was the main target, the resulting duct obstruction causes dilatation of the main duct and its branches in the body and tail of the pancreas, and subsequently also fibrosis (Fig. 4). After months or some years this patient will, apart from pain, suffer from severe exocrine and endocrine pancreatic insufficiency. When the damage was limited to the body and/or tail, the patient, even with abstinence from alcohol, may suffer from pain but will not develop pancreatic insufficiency, because of normal tissue remaining in the head of the pancreas (Fig. 4).

Conclusions

There are many reasons to believe that the necrosis-fibrosis sequence is the basic pathogenetic event in the evolution of chronic pancreatitis. This sequence implies that acute pancreatitis, probably in its severe relapsing form, may be the cause of chronic pancreatitis. To make

this concept relevant to the individual patient and the natural course of his/her disease, the extent and distribution pattern of necrosis in acute pancreatitis has to be carefully evaluated with regard to the restitutional processes (i.e. restitutio ad integrum, pseudocyst, intrapancreatic fibrosis) that may follow. Such an analysis reveals that only after severe acute pancreatitis and only under certain conditions, such as the occurrence of intrapancreatic necrosis involving the main duct, development of chronic pancreatitis can be anticipated. The individuality of each patient's pancreatitis demands a thorough clinical and morphological assessment of the pancreas in order to assign the appropriate therapy to this disease and halt its progression (Warshaw 1990).

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