PANCREATIC AND HEPATOBILIARY DISORDERS IN INFLAMMATORY BOWEL DISEASE

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OU LU 2000
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Abstract
Extraintestinal manifestations in inflammatory bowel disease (IBD) have been described with varying frequencies. The aim of this study was to estimate the prevalence of pancreatic duct abnormalities, exocrine and endocrine dysfunction, elevated pancreatic enzymes, hepatobiliary disease, coexisting cholangiographic and pancreatographic duct changes, and elevated serum levels of fibrosis markers in IBD, and to correlate the findings with clinical, endoscopic and histologic variables.

From a local patient register, 237 patients were randomly selected and studied. Of these, 170 had ulcerative colitis (UC), 46 had Crohn’s disease (CD), and 21 had indeterminate colitis (IC). A detailed history was obtained from medical records and in a face-to-face interview. The patients were screened with a para-aminobenzoic acid (PABA) test and, for pancreatic enzymes, liver function tests, serum aminoterminal propeptide of type III procollagen (PIIINP), and laminin. Further pancreatic evaluation included endoscopic retrograde cholangiopancreatography (ERCP), ultrasound (US), secretin test, and glucagon C-peptide test. Further hepatobiliary evaluation consisted of ERCP, US, and liver biopsy.

In IBD, the prevalence rates of pancreatic duct abnormalities and exocrine dysfunction were 8% and 4%, respectively. Parallel impairment of exocrine and endocrine functions was shown. Acute idiopathic pancreatitis may complicate IBD. About 7-17% presented with elevated pancreatic enzymes. Enzyme elevation was associated with extensive and histologically active disease and, in some cases, with primary sclerosing cholangitis (PSC). Abnormal liver test results were commoner in patients with CD than in patients with UC (30% versus 11%). The prevalence of PSC in IBD was 11%, which is higher than previously reported (3.7-7.5%). PSC was commoner in patients with CD than in patients with UC (17.4% versus 7.6%). About half of the PSC patients had concomitant pancreatic duct changes, and the prevalence of concurrent cholangiographic and pancreatographic duct changes in IBD was 4.6%. Both serum PIIINP and laminin were increased in IBD patients. This was not only seen in patients with hepatobiliary disease and PSC, but also in patients with pancreatic disease.

In conclusion, pancreatic and hepatobiliary complications in IBD occur with high and similar frequencies in all IBD categories and are associated with each other. They are not clearly associated with the clinical course of IBD.

Keywords: collagen markers, pancreatic enzymes, primary sclerosing cholangitis.
To my family
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Vaasa, August 2000

Bengt Heikius
Abbreviations

ALAT  alanine aminotransferase
ALP   alkaline phosphatase
5-ASA 5-aminosalicylic acid
ASAT  aspartate aminotransferase
BMI   body mass index
CD    Crohn’s disease
CHG   cholangiographic
CHPG  cholangiopancreatographic
CP    chronic pancreatitis
CT    computed tomography
ERCP  endoscopic retrograde cholangiopancreatography
ERC   endoscopic retrograde cholangiography
ERP   endoscopic retrograde pancreatography
HBD   hepatobiliary disease
HSCc  hepatic stellate cells
IBD   inflammatory bowel disease
IC    indeterminate colitis
IQR   interquartile range
MRCP  magnetic resonance cholangiopancreatography
MRI   magnetic resonance imaging
NBT-PABA N-benzoyl-L-tyrosyl-p-aminobenzoic acid
NHBD  no hepatobiliary disorder
OGT   oral glucose tolerance test
PAB   pancreatic antibody
PABA  para-aminobenzoic acid
PIIIINP aminoterminal propeptide of type III procollagen
PSC   primary sclerosing cholangitis
PSCc  pancreatic stellate cells
UC    ulcerative colitis
UNL   upper normal limit
US    ultrasound, ultrasonography
List of original communications

This thesis is based on the following articles, which are referred to in the text using the Roman numerals I-IV:


Contents

Abstract
Acknowledgements
Abbreviations
List of original communications
1. Introduction .................................................................................................................. 15
2. Review of the literature ............................................................................................... 17
   2.1. Extraintestinal manifestations of inflammatory bowel disease (IBD) .................. 17
   2.1.1. General aspects ................................................................................................. 17
2.2. Hepatobiliary disease in IBD .................................................................................... 19
   2.2.1. Primary sclerosing cholangitis (PSC) ............................................................... 19
   2.2.2. Fatty liver ........................................................................................................ 22
   2.2.3. Chronic hepatitis and primary biliary cirrhosis .................................................. 22
2.3. Pancreatic disorders in patients with IBD ............................................................... 22
   2.3.1. Different forms of chronic pancreatitis .............................................................. 22
   2.3.2. Endocrine pancreatic insufficiency .................................................................... 24
   2.3.3. Pancreatic disorder in patients with UC ............................................................ 24
   2.3.4. Pancreatic disorder in patients with CD ............................................................ 24
   2.3.5. Pancreatic disorder in patients with PSC and IBD ............................................ 25
   2.3.6. Hyperamylasemia in patients with IBD ............................................................ 25
   2.3.7. Drug-induced pancreatitis in patients with IBD ............................................... 26
   2.3.8. Etiopathogenesis of IBD-associated pancreatic disorder .................................. 26
2.4. Diagnosis of chronic pancreatitis ............................................................................ 26
   2.4.1. Morphologic diagnosis ..................................................................................... 26
   2.4.2. Diagnostic tests for chronic pancreatitis ......................................................... 29
   2.4.3. Endocrine function tests .................................................................................. 31
2.5. Use of aminoterminal propeptide of type III procollagen and laminin in screening for hepatobiliary and pancreatic disorders .................................................. 32
   2.5.1. Hepatic fibrogenesis ....................................................................................... 32
   2.5.2. Pancreatic fibrogenesis .................................................................................... 33
3. Purpose of the present study ....................................................................................... 34
4. Patients and methods .................................................................................................. 35
4.1. Patients..................................................................................................................... 35
4.2. Methods

4.2.1. Pancreatic screening

4.2.2. Further pancreatic evaluation

4.2.3. Hepatobiliary screening

4.2.4. Further hepatobiliary evaluation

4.2.5. Measurements of the markers of connective tissue metabolism

4.2.6. Formation of subgroups of IBD patients with and without hepatobiliary and/or pancreatic abnormalities

4.3. Medical history of the patients

4.4. Histological evaluation of IBD

4.5. Ethical consideration

4.6. Statistical methods

5. Results

5.1. Pancreatic duct abnormalities and pancreatic function in patients with chronic IBD (I)

5.1.1. Primary screening investigation

5.1.2. Further pancreatic evaluation

5.2. Hepatobiliary and concurrent pancreatic duct abnormalities in patients with IBD (II)

5.2.1. Patients with abnormal liver test results

5.2.2. Summarized ERCP results of the whole study group

5.2.3. Liver histology

5.2.4. Liver histology combined with ERC changes

5.3. Elevated pancreatic enzymes in IBD are associated with extensive disease (III)

5.3.1. Disease extent, disease activity, previous bowel resections, and pancreatic enzymes

5.3.2. Group with elevated pancreatic enzymes

5.3.3. Smoking and drinking habits and pancreatic enzymes

5.3.4. Use of medication and pancreatic enzymes

5.3.5. Pancreatic enzymes in patients with increased liver enzymes and PSC

5.4. Elevated serum aminoterminal propeptide of type III procollagen (PIIINP) and laminin in IBD indicate hepatobiliary and pancreatic disorders (IV)

5.4.1. Association of the clinical characteristics and markers of connective tissue metabolism

5.4.2. PIIINP and laminin in IBD-associated hepatobiliary disorder

5.4.3. PIIINP and laminin in PSC

5.4.4. PIIINP and laminin and liver histology

5.4.5. PIIINP and laminin in patients with IBD-associated pancreatic disorder

5.4.6. PIIINP and laminin and pancreatic duct changes

5.4.7. PIIINP and laminin in patients with both hepatobiliary and pancreatic disorders

5.4.8. PIIINP and laminin in patients without hepatobiliary or pancreatic disorder

6. Discussion

6.1. Study population

6.2. Methods
6.2.1. Original study I ................................................................. 60
6.2.2. Original studies II-IV .......................................................... 62
6.3. Pancreatic duct abnormalities and pancreatic function in patients with chronic
    IBD (I) ...................................................................................... 62
    6.3.1. Pathogenesis ..................................................................... 63
6.4. Hepatobiliary and concurrent pancreatic duct abnormalities in patients
    with IBD (II) .............................................................................. 63
    6.4.1. Hepatobiliary disease ......................................................... 63
    6.4.2. Primary sclerosing cholangitis .......................................... 63
    6.4.3. Concomitant pancreatic duct changes in hepatobiliary disease ... 64
6.5. Elevated pancreatic enzymes in IBD are associated with extensive disease (III) .... 66
6.6. Elevated serum aminoterminal propeptide of type III procollagen (PIIINP) and
    laminin in IBD indicate hepatobiliary and pancreatic disorders (IV) .............. 68
6.7. Clinical implications ................................................................... 70
7. Conclusions ................................................................................ 71
8. References .................................................................................. 73
1. Introduction

The two main categories of inflammatory disorders of the gastrointestinal tract are ulcerative colitis (UC) and Crohn’s disease (CD), collectively called inflammatory bowel disease (IBD). They are chronic relapsing and remitting inflammatory gastrointestinal disorders of unknown etiology. UC involves mainly the superficial layers of the bowel, is limited to the colon, and is not associated with granulomas. CD, in contrast to UC, is characterized by transmural, patchy, granulomatous inflammation of any part of the gastrointestinal tract, although it is most common in the ileocaecal area. CD also involves strictures and fistula formation. In some cases of colitis, no distinction between UC and CD can be made, and these patients are classified as having indeterminate colitis (IC).

IBD may affect persons of all ages, with a major peak in the third decade. Although inflammatory bowel diseases primarily involve the bowel, they are also associated with manifestations in other organ systems. In some patients, these extraintestinal manifestations may be more problematic than the bowel disease itself.

Hepatobiliary diseases are common extraintestinal manifestations associated with IBD. The most common hepatobiliary disorder in IBD patients is primary sclerosing cholangitis (PSC), a syndrome of unknown origin characterized by chronic fibrosing inflammation of both intrahepatic and extrahepatic bile ducts with insidious and unpredictable progression (LaRusso et al. 1984). PSC has been reported mostly in UC, but infrequently in CD, and the association between PSC and CD has been questioned.

Pancreatic ductal involvement in PSC has been reported with highly variable frequencies from 0% to 77%. Lindström et al. (1990) documented an average frequency of about 20%, but the patients have usually been selected, and the proportion of IBD associated PSC has varied widely. The true prevalence of concurrent hepatobiliary and pancreatic duct abnormalities remains undetermined.

Both pancreatitis and pancreatic insufficiency may occur as extraintestinal manifestations of IBD (Seyrig et al. 1985, Matsumoto et al. 1989, Niemelä et al. 1989, Piontek et al. 1990). Most of the cases have been seen in patients with CD (Legge et al. 1971, Altman et al. 1983, Meltzer & Koreliz 1988, Hegnhøj et al. 1990), but pancreatic abnormalities have also been reported in patients with UC (Forbes et al. 1987, Lysy & Goldin 1992), especially ones with concomitant PSC (Børkje et al. 1985, Lindström et
al. 1990). The true prevalence of pancreatic duct abnormalities in IBD is yet to be determined.

Drugs used in the treatment of IBD (azathioprine, 6-mercaptopurine and 5-ASA) may occasionally cause acute pancreatitis, but the prevalence is very low. In most cases, no etiological factors predisposing to pancreatic abnormalities have been found other than the IBD itself.

The determination of serum amylase and lipase is used to support the diagnosis of pancreatitis. Hyperamylasemia has earlier been found in 8%–21% of selected IBD patients without any relationship to the activity, duration, or extent of the disease (Katz et al. 1988, Tromm et al. 1991).

The diagnosis of PSC is based on both endoscopic retrograde cholangiography (ERC) and liver biopsy findings (Chapman et al. 1980). Both of these diagnostic procedures are invasive and involve a risk of complications. Therefore, there has been an intensive search for noninvasive and yet reliable diagnostic methods capable of detecting hepatobiliary diseases. The serum aminoterminal propeptide of procollagen type III (PIIINP) has been widely considered the most reliable serum marker of ongoing fibrosis and inflammatory activity in chronic liver disease (Wu & Danielsson 1995). Recently, serum PIIINP has also been shown to be elevated in patients with UC and PSC (Leidenius et al. 1997). Laminin, another marker of fibrosis, is one of the main glycoproteins in basement membranes with an important role in cellular adhesion and differentiation. Increased serum laminin levels have been found in patients with hepatic fibrosis and cirrhosis, showing an association with the extent of fibrotic transition in the liver (Wu & Danielsson 1995). As yet, there are no reports of serum laminin in IBD. The usefulness of circulating PIIINP or laminin as an index of pancreatic injury in pancreatic disease associated with IBD has not been studied.
2. Review of the literature

2.1. Extraintestinal manifestations of inflammatory bowel disease.

2.1.1. General aspects

Many extraintestinal manifestations are associated with UC and CD (Table 1) (Andres & Friedman 1999). In about one-third of the patients with IBD, a variety of inflammatory

Table 1. Extraintestinal manifestations of inflammatory bowel disease.

<table>
<thead>
<tr>
<th>Manifestation</th>
<th>Ulcerative colitis (%)</th>
<th>Crohn’s disease (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arthritic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute arthropathy</td>
<td>10–15</td>
<td>15–20</td>
</tr>
<tr>
<td>Sacroileitis</td>
<td>9–11</td>
<td>9–11</td>
</tr>
<tr>
<td>Ankylosing spondylitis</td>
<td>1–3</td>
<td>3–5</td>
</tr>
<tr>
<td>Dermatologic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erythema nodosum</td>
<td>10–15</td>
<td>15</td>
</tr>
<tr>
<td>Pyoderma gangrenosum</td>
<td>1–2</td>
<td>1–2</td>
</tr>
<tr>
<td>Ocular</td>
<td>5–15</td>
<td>5–15</td>
</tr>
<tr>
<td>Hepatobiliary</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary sclerosing cholangitis</td>
<td>2–7.6</td>
<td>1</td>
</tr>
<tr>
<td>Choledocholithiasis</td>
<td>—</td>
<td>15–30</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nephrolithiasis</td>
<td>—</td>
<td>5–10</td>
</tr>
<tr>
<td>Amyloidosis</td>
<td>—</td>
<td>Rare</td>
</tr>
</tbody>
</table>
conditions affecting other organ systems may occur at some point during the course of the disease (Greenstein et al. 1976, Danzi 1988). The conditions are much more common in patients with extensive colitis than in those with left-sided colitis or proctitis (Monsen et al. 1990). These manifestations are thought to be due to the circulating immune complexes induced by antigens that are derived from the gut lumen or the damaged bowel mucosa. In support of this notion, most of the conditions disappear when the patients undergo a total colectomy (Cangemi et al. 1989).

The most common manifestation is acute arthropathy, which may affect up to 20% of patients (Loftus et al. 1977). Orchard et al. (1998) found pauciarticular arthritis in 3.5% of patients with UC and observed that clinical flares of arthritis generally paralleled the activity of the bowel disease, whereas articlar symptoms in patients with small-joint polyarthritis persisted independent of the clinical activity of colitis. Sacroilitis and ankylosing spondylitis are less common than peripheral arthropathy (Levine & Lukawski-Trubish 1995). The majority of patients with sacroilitis are HLA-B27-negative and do not progress to ankylosing spondylitis. Contrariwise, 80% of UC patients with ankylosing spondylitis are HLA-B27-positive. The course of the spondylitis is independent of the activity of the bowel disease (Jewell 1998).

Ocular complications include anterior uveitis and episcleritis and occur in 5% to 15% of IBD patients. The course of these complications tends to parallel that of the underlying bowel disease (Andres & Friedman 1999).

The most common dermatologic manifestation is erythema nodosum, arising in up to 15% of IBD patients, often in association with peripheral arthropathy (Levine & Lukawski-Trubis 1995). Pyoderma gangrenosum is a less common dermatologic complication, which tends to parallel the activity of the bowel disease (Jewell 1998), but may persist despite resection of colitis.

The frequencies of dermatologic, arthritic, and ocular complications are almost similar in both forms of IBD. Several additional complications are unique to CD patients as a consequence of either the ulcerative nature of CD or the small intestine involvement. Patients with terminal ileal disease or resection are at risk for bile acid malabsorption, which may result in the formation of gallstones. Gallstones develop in 15% to 30% of patients with small bowel CD. The stones are predominantly cholesterol gallstones (Cohen et al. 1971). Oxalate nephrolithiasis occurs in 5% to 10% (Andres & Friedman 1999). It is usually the result of fat malabsorption that occurs concomitantly with small bowel CD. Dietary calcium binds to malabsorbed fatty acids in the colonic lumen, and free oxalate is absorbed. This situation results in hyperoxaluria and oxalate stones (McLeod & Churchill 1992). Amyloidosis in patients with CD is rare.

Osteopenia has also been reported in patients with IBD. Especially IBD patients with high cumulative lifetime corticosteroid doses, patients with active Crohn’s disease and female smokers with IBD show reduced bone mineral density (Silvennoinen 1996).

Thromboembolic disease is an extraintestinal manifestation attributed to the hypercoagulable state that parallels disease activity and manifests as thrombocytosis, elevated plasma fibrinogen, factor V, factor VIII, and decreased plasma anti-thrombin III. This state may lead to deep venous thrombosis, pulmonary emboli, and neurovascular disease (Hofley & Piccoli 1994).
2.2. Hepatobiliary disease in IBD

The most common extraintestinal manifestations associated with IBD are hepatobiliary diseases, which present as abnormal liver tests. The prevalence of patients with laboratory signs of hepatobiliary disease in UC and CD varies considerably. For UC, the prevalence figures range from 3% to 17% (Perrett et al. 1971, Dew et al. 1979, Shepard et al. 1983, Wewer et al. 1991, Broomé et al. 1994). In a Finnish study, almost 30% of UC patients had had abnormalities in their liver biochemistry at least once during their disease (Aitola et al. 1994). For CD, the prevalence figures range from 8% (Lind et al. 1985) to 30% (Wewer et al. 1991). Pathologic findings in liver biopsy specimens obtained at colectomy have been reported in up to 94% of patients with UC (Eade 1970). In a more recent study, 34% of patients with routine liver biopsy at colectomy had changes in their liver histology (Aitola et al. 1994). These findings include steatosis, nonspecific reactive hepatitis and sclerosing cholangitis. Morphological liver abnormalities may be present despite normal liver function values in patients with IBD (Dorbal et al. 1967, Perret et al. 1971, Broomé et al. 1990, Aitola et al. 1994).

2.2.1. Primary sclerosing cholangitis

The most common form of hepatobiliary manifestation in IBD is sclerosing cholangitis (PSC), a chronic, progressive, cholestatic liver syndrome of unknown etiology. It is characterized by persistent inflammation, obliterative fibrosis and segmental dilatation of intrahepatic and extrahepatic bile ducts and shows insidious and unpredictable progression (Chapman et al. 1980, Shepherd et al. 1983, Wiesner et al. 1985). The disease usually progresses and results in cirrhosis, portal hypertension, and liver failure, ultimately necessitating liver transplantation (Kaplan 1997). The cause of PSC remains unknown. It is most likely to be caused by multiple factors, including immunologic injury, portal bacteremia, and chronic bile duct infection.

The pathognomonic finding on liver biopsy, albeit rarely seen, is the onion skin lesion, consisting of concentric rings of dense connecting tissue that surround a necrotic, often totally obliterated bile duct (Ludwig et al. 1981). These lesions cause bile duct strictures, the cholangiographic finding required for the diagnosis (Wiesner & LaRusso 1980). Alternating strictures and dilatations give affected bile ducts the beaded appearance at ERC that is characteristic of the disease.

Many studies have shown a prevalence of PSC ranging from 2.4% to 7.5% in patients with IBD (Olsson et al. 1991, Schrumpf et al. 1980). In an unselected Swedish patient population of 1500 patients with UC, it was reported to be 3.7%, which is the largest figure reported thus far (Olsson et al. 1991). When only patients with substantial colitis were included, the corresponding figure was 5.5%. In a recent study on selected patients, the prevalence of PSC in UC was notably high, 26%, clearly due to selection bias, as pointed out by the authors (Boberg et al. 1994).

Approximately 75% of PSC patients have IBD, most commonly UC. IBD usually precedes the diagnosis of PSC. The liver disease may occur after proctocolectomy, and
colitis may develop several years after the onset of PSC (Cangemi et al. 1989). The association between PSC and CD has been questioned, as few cases with this combination have been reported. In 1987, however, a Norwegian study suggested that PSC is seen equally frequently in CD as in UC (Aadland et al. 1987). In a recent retrospective study of IBD-associated PSC patients from Sweden, 8% had CD (Broomé et al. 1996). In another study, PSC was reported to be the major hepatic disease in patients with CD and abnormal liver function results, with an overall prevalence of 3.4% (Rasmussen et al. 1997). The prevalence of PSC in patients with colonic CD was 9%. The true frequency of PSC in IBD patients may actually be higher, since many patients may be asymptomatic and without laboratory abnormalities (Aadland et al. 1987).

The diagnosis of PSC has increased dramatically in the last 20 years because of increased clinical awareness and utilization of diagnostic tests, such as ERCP, rather than a true increase in the incidence of the disease. About 70% of patients are male, and the average age at the time of diagnosis is 40 years (Wiesner & LaRusso 1980, Olsson et al. 1991).

Disease severity varies from asymptomatic with normal or minimally elevated serum alkaline phosphatase levels to secondary biliary cirrhosis, which may be complicated by liver failure and portal hypertension. The onset of symptoms is usually insidious. The most common presenting symptoms include pruritus, fatigue, and right upper quadrant abdominal discomfort. Both symptomatic and asymptomatic patients with PSC have shorter survival compared to age-, sex-, and race-matched controls (Porayko et al. 1990). Predicting survival on the basis of the clinical, biochemical, and histological features of PSC is important for determining the optimal timing of liver transplantation, for monitoring the outcome of therapeutic interventions, and for counseling patients about the likely rate of disease progression (Farrant et al. 1991, Dickson et al. 1992).

Liver function tests usually reveal elevated serum alkaline phosphatase levels (>3 times normal in 85%), mild-to-moderate elevations of serum aspartate aminotransferase and alanine aminotransferase, and elevated serum bilirubin (50% to 60%) (Chapman et al. 1980, Wiesner & LaRusso 1980, Balasubramanian et al. 1988).

Cholangiography remains the gold standard for the diagnosis of PSC. ERCP is the preferred method, although transhepatic cholangiography can also be used for ERCP failures. Cholangiography classically shows multiple strictures of varying lengths with intervening dilated segments producing a beaded appearance of intrahepatic and extrahepatic bile ducts. A classification system of cholangiographic findings has been proposed by Majoie et al. (1991).

Magnetic resonance cholangiopancreatography (MRCP) has been progressively tested in patients with PSC. It was comparable with either ERCP or transhepatic cholangiography in establishing the diagnosis in PSC patients (Ernst et al. 1997). Moreover, MRCP allowed visualization of obstructed ducts, usually not opacified by ERCP. However, larger studies are required before MRCP can be fully evaluated in the diagnosis of PSC (Martins & Chapman 1998). Three-dimensional helical computed tomography with intravenous cholangiography has also been used in the diagnosis of morphological changes in the biliary tree, when ERCP has been unsuccessful (Hase et al. 1997).
The diagnostic histological abnormality in PSC is fibrous obliterator cholangitis. The end stage of the disease is marked by histological findings that include ductopenia and biliary cirrhosis (Table 2).

Table 2. Histological staging of primary sclerosing cholangitis.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Histological findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>I (portal)</td>
<td>Portal edema, inflammation, and ductal proliferation;</td>
</tr>
<tr>
<td>II (periportal)</td>
<td>Periportal fibrosis, inflammation with/without ductular proliferation; lymphocytic piecemeal necrosis may be present</td>
</tr>
<tr>
<td>III (septal)</td>
<td>Fibrous septa extend between portal tracts; more prominent ductopena; biliary piecemeal necrosis</td>
</tr>
<tr>
<td>IV (cirrhotic)</td>
<td>Irregular regenerative nodules, ductular and piecemeal necrosis, loss of interlobular bile ducts</td>
</tr>
</tbody>
</table>

Modified from Ludwig (1989)

PSC has been subdivided into three categories based on the cholangiographic and hepatic histology findings. Global or classic PSC is the most common variety of the syndrome and involves the bile ducts, both inside and outside the liver. Both liver biopsy and cholangiogram show typical abnormalities. In small-duct PSC (formerly termed pericholangitis), the cholangiogram may be normal, but the liver biopsy shows evidence of obliterator cholangitis. In large-duct PSC, the cholangiogram is diagnostic, although the liver biopsy may show minimal or nonspecific changes (Table 3) (Ludwig 1991).

At present, there is no effective medical treatment for the disease. Despite the fact that its efficacy has not been proved, ursodeoxycholic acid is widely used to treat PSC. In 1997, Lindor reported on a large study of long duration in which ursodeoxycholic acid had no beneficial effect on the course of the disease or on the time from diagnosis to liver transplantation, but the biochemical profiles were improved.

Table 3. Duct disease classification for the primary sclerosing cholangitis (PSC) syndrome.

<table>
<thead>
<tr>
<th>Diagnostic terminology</th>
<th>Cholangiography</th>
<th>Liver biopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large-duct PSC (extrahepatic or intrahepatic)</td>
<td>Typical findings</td>
<td>Not diagnostic</td>
</tr>
<tr>
<td>Small-duct PSC (pericholangitis)</td>
<td>Not diagnostic</td>
<td>Typical findings</td>
</tr>
<tr>
<td>Combined large and small duct PSC (global PSC)</td>
<td>Typical findings</td>
<td>Typical findings</td>
</tr>
</tbody>
</table>

A variety of endoscopic, percutaneous, radiologic, and surgical techniques are used to treat the complications of mechanical obstruction that results from progression of the disease. The only treatment for patients with end-stage disease is liver transplantation. The five-year survival after liver transplantation has been almost 90% (Farges et al. 1995, Narumi et al. 1995).

Cholangiocarcinoma is the most serious complication of PSC. Its incidence ranges from 6% to 14% (Wee et al. 1985, Schrumpf et al. 1994, Broomé et al. 1996). The incidence is highest in patients with cirrhosis and in patients with long-standing UC. The only definite treatment is surgical resection, but long-term survival is poor. Of interest are recent data suggesting that patients with UC and concomitant PSC have a higher risk for colonic dysplasia and colorectal cancer than those with UC alone (Ahnen 1996, Leidenius et al. 1997, Kornfeld et al. 1997).

### 2.2.2. Fatty liver

Fatty changes are seen commonly in liver biopsy specimens from patients with UC and CD. This change is usually asymptomatic and reversible and often reflects the duration and severity of the underlying IBD. Malnutrition, protein loss, anemia, and corticosteroid medication may be contributing factors (Raj & Lichtenstein 1999).

### 2.2.3. Chronic hepatitis and primary biliary cirrhosis

There is an increased incidence of chronic hepatitis in patients with IBD, particularly in UC (Wee & Ludwig 1985). It is believed to be autoimmune in nature and is characterized by portal tract inflammation of variable activity in the form of piecemeal necrosis. The diagnosis may be confusing because similar histologic changes are occasionally seen in PSC.

Thirteen cases of concurrent primary biliary cirrhosis and UC have been reported in the literature so far. The prevalence of primary biliary cirrhosis seems to be at least 30 times higher in patients with UC than in the general population (Koulentaki et al. 1999).

### 2.3. Pancreatic disorders in patients with IBD

#### 2.3.1. Different forms of chronic pancreatitis

In the 1988 Marseille-Rome symposium, chronic pancreatitis (CP) was defined as ‘the presence of chronic inflammatory lesions characterized by the destruction of exocrine parenchyma and fibrosis and, at least in the late stages, the destruction of endocrine parenchyma’ (Sarles 1992).
The pathogenesis of chronic pancreatitis is poorly understood. According to the recent “necrosis-fibrosis” hypothesis, chronic pancreatitis is the result of relapsing severe acute pancreatitis (Klöppel & Maillot 1998). Interstitial fat necrosis and hemorrhage seem to induce peribular fibrosis. This fibrotic process gradually results in duct occlusions and strictures. The ducts, once altered, hamper the flow of pancreatic secretions, thereby enabling precipitation of proteins, with subsequent calcification and ductal obstruction.

There are several etiologic factors to be considered in the development of chronic pancreatitis (Table 4), but in the Western countries, chronic alcoholism is undoubtedly the major cause, underlying 70% to 90% of cases. The incidence of acute pancreatitis increased by 58% in Finland (from 47 to 73/100,000/year) during 1972-89, and the increase is directly related to the increase in alcohol consumption (Jaakkola & Nordback 1993). As to the consequences of acute recurrent alcohol-induced pancreatitis/chronic pancreatitis, two main theories still exist: 1) acute recurrent pancreatitis gradually destroys the gland, resulting in chronic pancreatitis, and 2) chronic pancreatitis is the underlying disease, and the acute pancreatitis only represents an acute aggravation of this chronic disease (Sarles et al. 1993, Ammann & Muellhaupt 1994, Ammann et al. 1996).

<table>
<thead>
<tr>
<th>Type</th>
<th>Etiologic factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic calcifying</td>
<td>Alcohol, hereditary, tropical, hyperlipoproteinemia, hypercalcemia, idiopathic, drugs</td>
</tr>
<tr>
<td>Chronic obstructive</td>
<td>Pancreatic tumors, postpancreatic ductal strictures, e.g., gallstones, pancreas divisum</td>
</tr>
<tr>
<td>Chronic inflammatory</td>
<td>Unknown</td>
</tr>
<tr>
<td>Chronic autoimmune</td>
<td>Associated with autoimmune disorders, e.g., primary sclerosing cholangitis, Sjögrens’s syndrome, primary biliary cirrhosis, sclerosing pancreatitis (in cystic fibrosis)</td>
</tr>
</tbody>
</table>

Chronic calcifying pancreatitis accounts for 95% of the cases of chronic pancreatitis. The ducts are irregular, often focally strictured or beaded, and carry proteinaceous plugs, either with or without calcification. Obstructive pancreatitis is due to severe narrowing or occlusion of the main pancreatic duct or its side branches due to a tumor, scarring, pseudocysts or gallstones. Pancreatitis has been described in many autoimmune disorders, such as Sjögren’s syndrome (Lindström et al. 1991), primary biliary cirrhosis (Epstein et al. 1982) and PSC (Bastid et al. 1990). The pathology of this painless and often asymptomatic pancreatic affliction is incompatible with that described in classical chronic pancreatitis, and the term ‘chronic autoimmune pancreatitis’ has been suggested for this form of CP (Chari & Singer 1994).
2.3.2. Endocrine pancreatic insufficiency

The occurrence of diabetes in a given form of chronic pancreatitis depends on the type of the lesion and the duration of the disease. In the most frequent form, chronic calcifying pancreatitis, diabetes is an almost universal complication (Sarles 1992). In a longitudinal study of 335 patients with exocrine pancreatic insufficiency, 8% had diabetes, half of whom required insulin treatment at the baseline (Lankisch et al. 1993). After 10 years, the incidence of diabetes had increased 10-fold: 78% suffered from diabetes and 40% required insulin.

2.3.3. Pancreatic disorder in patients with UC

The first suggestion of a significant connection between pancreatic inflammation and IBD was reported in 1950 by Ball et al., who found chronic pancreatitis in 46 (54%) of 86 patients with UC post mortem, although none had shown clinical evidence of pancreatic disease. The list of extraintestinal manifestations of UC does not usually include pancreatitis or pancreatic insufficiency. However, several reports have mentioned this association (Seyrig et al. 1985, Forbes et al. 1987). Since then, an increasing number of pancreatic abnormalities in patients with IBD have been reported (Lysy & Goldin 1992). Chronic pancreatitis and PSC or pericholangitis have been reported to occur before or soon after the onset of UC (Axon et al. 1979, Epstein et al. 1982, Gurian & Keefe 1982, Seyrig et al. 1985, Borkje et al. 1985). Patients with both UC and CD seem to be at an increased risk for acute pancreatitis (Rasmussen et al. 1999).

2.3.4. Pancreatic disorder in patients with CD

Chapin et al. (1956) found mild-to-moderate pancreatic fibrosis at autopsy in 38% of 39 patients with CD and in 3% of healthy controls. Seidman et al. (1983) reported two cases of CD associated with acute pancreatitis in 1983. Pancreatic antibodies (PABs) studied by immunofluorescence on sections of human pancreas have been found to occur in about one third of patients with CD. Exocrine pancreatic function was impaired significantly more often in PAB-positive than PAB-negative CD patients (Seibold et al. 1996). Seyrig et al. (1985) reported six cases of CD with acute pancreatitis of unknown origin. Meyer et al. (1987) reported a female case of CD with acute pancreatitis. The secretin-cerulein test showed a bicarbonate plus enzyme or an enzyme insufficiency in six (24%) of the 17 patients with CD (Angelini et al. 1988). Matsumoto et al. (1989) also reported two cases of CD coincident with acute pancreatitis, and speculated that pancreatitis may be an extraintestinal complication of CD. Tromm et al. (1991) reported painless hyperamylasemia in 18 of 114 patients with CD (16%).
2.3.5. Pancreatic disorder in patients with PSC and IBD

Pancreatic ductal involvement in IBD-associated PSC has earlier been reported with highly variable frequencies from 0% to 77% (Epstein et al. 1982, MacCarty et al. 1983, Palmer et al. 1984, Børkje et al. 1985, Aadland et al. 1987) and an average frequency of about 20% (Lindström et al. 1990). The patients, however, have been selected, and the proportion of IBD-associated PSC has varied widely. A schematic representation of changes in both bile and pancreatic ducts is shown in Fig. 1.

2.3.6. Hyperamylasemia in patients with IBD

Katz et al. (1988) reported hyperamylasemia without evidence of pancreatitis in 8% of patients with CD. Tromm et al. (1991) found painless hyperamylasemia or hyperlipasemia in 16% of patients with CD and in 21% of patients with UC in a prospective study of selected patients. They found no relation to either the activity and duration of the disease or drug treatment. Nor did they find any relation to disease extent, except for a higher frequency of hyperenzymemia in Crohn’s colitis compared to ileitis or ileocolitis.

Fig. 1. Schematic representation of changes in sclerosing cholangitis. The thick black areas indicate sites of the biliary tree and pancreatic duct involvement. Adapted from Lefkowitz JH (1982) Primary sclerosing cholangitis. Arch Intern Med 142:1157-1160.
2.3.7. Drug-induced pancreatitis in patients with IBD

The diagnosis of drug-induced acute pancreatitis is difficult to establish. Although a positive rechallenge with a drug is the best evidence available for cause and effect, it is not a positive proof (Tenner & Steinberg 1988). 5-aminosalicylate (5-ASA) preparations and sulfasalazine have been implicated as causing mild acute pancreatitis, and case reports with rechallenges have been described, but the prevalence is very low (Mallory & Kern 1988). Three of four case reports of metronidazole-induced acute pancreatitis have had positive rechallenges (Tenner & Steinberg 1998). Azathioprine and its metabolite, 6-mercaptopurine, have strong evidence implicating them as agents that cause acute pancreatitis. Almost 6% of patients treated with azathioprine and 3% of those treated with 6-mercaptopurine developed acute pancreatitis (Present et al. 1980, Haber et al. 1986). The causal relationship between corticosteroids and acute pancreatitis remains largely unproved (Mallory & Kern 1980).

2.3.8. Etiopathogenesis of IBD-associated pancreatic disorder

Piontek et al. (1990) has proposed the following etiopathogenetic conditions as contributing factors to pancreatic involvement in IBD:

1) Drugs, such as 5-ASA, sulfasalazine, azathioprine, and 6-mercaptopurine.

2) Duodenal reflux into pancreatic ducts via an inflamed, incompetent, and stenotic ampulla of Vater could be a mechanism in CD-associated pancreatitis. Direct ampullary involvement by the disease may also cause intermittent obstruction of pancreatic flow.

3) Small gallstones or sludge have been found to be responsible for at least some cases of pancreatitis in IBD (Lee et al. 1992). Pancreatic duct abnormalities have been reported in nearly half of the patients with gallstone disease (Misra et al. 1990).

4) The presence of autoantibodies against an exocrine pancreas tested by indirect immunofluorescence has been reported in 31-39% of patients with CD, suggesting an immunologic basis as the etiology (Stöcker et al. 1987, Seibold et al. 1991, Seibold et al. 1996).

2.4. Diagnosis of chronic pancreatitis

2.4.1. Morphologic diagnosis

The most commonly used techniques in the diagnosis of chronic pancreatitis (CP) are a plain abdominal radiograph, ultrasonography, computed tomography (CT), and ERCP. New techniques, such as endoscopic ultrasound, magnetic resonance imaging, and pancreatic Trucut biopsy, can be useful in certain circumstances, but are not yet widely available (Tytgat 1992). Currently, the Marseille-Cambridge classification is most often used.
2.4.1.1. Ultrasound and computed tomography

In current clinical practice, ultrasound is usually the first diagnostic step when pancreatic disease is suspected. CT is particularly useful when ultrasound examination fails because of severe meteorism (Lankisch & Banks 1998). Without discomfort to the patient, these studies enable the detection of gallstones and pancreatic calcifications and an evaluation of pancreatic pseudocysts and abscesses as well as the enlargement of the whole organ or parts of it. Both imaging procedures appear to be of similar value in detecting abnormalities of the pancreas itself.

In ultrasound, the usual pattern of parenchymal texture is that of heterogeneity and increased echogenicity. High-quality equipment allows visualization of the pancreatic duct system. Dilated pancreatic ducts are common in chronic pancreatitis. Although duct caliber can be appreciated to some extent, overall information about the ducts is less precise with ultrasound than with ERCP. Ultrasound and CT are also helpful in the detection of concomitant hepatic and biliary diseases and peripancreatic fluid collections (Tytgat 1992).

The reported sensitivities of ultrasound for CP range within 80%-90%, specificity being about 90% (Lankisch et al. 1990). Only one study has been done on the correlation of morphological findings in ultrasound with pancreatic function results. A distinct, but not very close correlation between the severity of functional impairment and the morphological picture of parenchymal destruction was found (Bolondi et al. 1986). Especially at the early stage of CP, functional impairment precedes morphological abnormalities.

The sensitivity and specificity of CT in patients with CP are about 90%, which is in the same range as in ultrasound (Lee 1986).

2.4.1.2. Magnetic resonance imaging (MRI)

Until recently, conventional MRI played a minor role in the evaluation of patients with CP. The availability of heavily T2w breath hold sequences changed the value of MRI. The pancreatic and bile ducts distal to the obstruction are identified routinely (Friedrich et al. 1998). At present, the sensitivity and specificity of MRCP are improving. Accordingly, MRCP has the potential to replace the most widely used ERCP as the primary diagnostic tool. We can therefore expect that, in the future, ERCP will be utilized less for diagnostic purposes and more for therapy maneuvers, such as pancreatic sphincterotomy, stricture dilatation and stenting, pseudocyst drainage, and endoscopic tissue sampling (Parsons & Carr-Locke 1998).

2.4.1.3. Endoscopic retrograde cholangiopancreatography (ERCP)

ERP demonstrates better than any other imaging procedure changes in the pancreatic duct system (i.e. the main pancreatic duct and its side branches) and the common bile duct.
Apart from pancreatic biopsy, ERP has been considered the most sensitive and specific test for the diagnosis of chronic pancreatitis, and this technique has become the gold standard against which all the other tests are evaluated. A meta-analysis of patients with chronic pancreatitis diagnosed with ERP suggested very high sensitivities and specificities (86% -90%) (Glaser 1990). Compared with hormonal stimulation tests, a sensitivity of up to 96% was found in another study (Girdwood et al. 1984).

**Table 5. Cambridge classification of pancreatograms in chronic pancreatitis (modified from Axon et al. 1984).**

<table>
<thead>
<tr>
<th>Terminology</th>
<th>Main duct</th>
<th>Abnormal side branches</th>
<th>Additional features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Normal</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Equivocal</td>
<td>Normal</td>
<td>Fewer than 3</td>
<td></td>
</tr>
<tr>
<td>Mild changes</td>
<td>Normal</td>
<td>3 or more</td>
<td></td>
</tr>
<tr>
<td>Moderate changes</td>
<td>Abnormal</td>
<td>More than 3</td>
<td>One or more: large cavity, obstruction, filling defects, severe dilatation or irregularity</td>
</tr>
<tr>
<td>Marked changes</td>
<td>Abnormal</td>
<td>More than 3</td>
<td></td>
</tr>
</tbody>
</table>

Serving as a basis for uniformity and comparative studies, the Cambridge classification (Table 5) grades pancreatograms from normal or equivocal to marked or severe CP (Axon et al. 1984). The diagnosis of CP is based on changes in both the main pancreatic duct and the side branches. The main duct changes are defined as dilation, narrowing or stricture formation, irregular contour, associated filling of cavities or pseudocysts, or filling defects. More subtle changes in the side branches include irregular contour, shortening, and dilation. It is desirable to obtain both a pancreatogram and a cholangiogram, since the anatomic relationships and pathologic changes in each system help to define the other (Tytgat 1992).

An abnormal ERP does not definitely establish the diagnosis of CP, and duct abnormalities that have turned out to be false-positive have been described. Changes in pancreatic ducts have been associated with aging (Kreel & Sandin 1973). Pancreatic secretion may be normal in a sizable fraction of the patients with radiological evidence of pancreatitis (Braganza et al. 1982, Angelini et al. 1984). Conversely, false-negative ERP results have also been reported, which means that a normal pancreatic duct on ERP does not exclude exocrine pancreatic insufficiency (Nakano et al. 1974, Dobrilla et al. 1976, Girdwood et al. 1984).

The correlation between ductal changes and functional impairment is good in patients with marked ductal abnormalities (Bozkurt et al. 1994), but less good in patients with minimal changes (Braganza et al. 1982). A study by Hayakawa et al. (1992) confirmed the superiority of hormonal stimulation tests over ERP in a group of patients with
histologically proven CP. The secretin test therefore appears able to diagnose CP at an earlier stage than any test of pancreatic structure (Lambiase et al. 1993). Some have even suggested that the gold standard in diagnosing CP could therefore be direct hormonal testing alone, rather than ERP (Forssmark & Toskes 1995). It seems that hormonal stimulation tests and ERP are complementary in diagnosing CP.

2.4.2. Diagnostic tests for chronic pancreatitis

2.4.2.1. Measurements of pancreatic enzymes in blood

In chronic pancreatitis, the serum enzyme levels (amylase, lipase, trypsin) may be elevated, normal or low, and in an acute exacerbation of the chronic process, the levels of pancreatic isoamylase and lipase are elevated in about 60% (Ventrucci et al. 1989).

The only tissue other than pancreas or salivary glands that may have a very high concentration of amylase is a neoplasm that produces amylase (Pieper-Bigelow et al. 1990). Hyperamylasemia is frequently present in patients with such conditions as perforated bowel, appendicitis, peritonitis, choledocholithiasis, pneumonia, and anorexia nervosa.

The finding of a subnormal serum concentration of pancreatic enzymes could be a valuable diagnostic indicator of chronic pancreatitis. The enzymes studied include pancreatic isoamylase (Skude & Eriksson 1976), lipase (Lesi et al. 1985), trypsin (Koop et al. 1980), and elastase (Del Favero et al. 1985). Although patients with end-stage chronic pancreatitis characteristically have low serum levels of these enzymes, the diagnosis is usually obvious on clinical grounds. Patients with mild-to-moderate pancreatic dysfunction often have normal or elevated serum enzyme concentrations (Owyang & Levitt 1995). Especially low serum isoamylase levels support the diagnosis of CP, whereas normal levels do not exclude the diagnosis (Lankisch & Banks 1998).

2.4.2.2. Measurement of pancreatic exocrine secretion.

Direct tests of secretory function

Direct tests of pancreatic secretory capacity involve collection of duodenal or pancreatic juice before and after hormonal pancreatic stimulation (Niederau & Grandell 1985, Li et al. 1989). For the collection of duodenal juice uncontaminated by gastric juice, several double- or multiple-lumen tubes have been recommended. The tests have not been standardized. Therefore, the test performance differs from center to center, each center having its own levels of normal values.

In the secretin test, only the maximal duodenal bicarbonate concentration and the volume of secretion are analysed as direct measures of both ductular and acinar pancreatic
function (Nordhekk 1998). In the secretin-cholecystokinin test, the combination of secretin with cholecystokinin provides information of both the secretory capacity of bicarbonate and the digestive enzymes, usually trypsin and/or amylase (both ductular and acinar function). In chronic pancreatitis, the secretion of enzymes may become impaired earlier than the secretion of bicarbonate (Lankisch et al. 1983).

The sensitivity of the direct secretin or secretin-cholecystokinin test depends primarily on the severity of the disease in the group of patients studied. Sensitivity values range from 74% to 97% in the literature. Reported values for specificity range from 80% to 98% (Li et al. 1989). False negatives are most likely to derive from mild cases, whereas false positives are seen in patients with coeliac disease, diabetes, subtotal gastrectomy, hepatic cirrhosis and biliary disease. Although intubation tests are invasive, inconvenient, expensive and time-consuming, direct secretory tests continue to be the most reliable method to estimate exocrine pancreatic function (Li et al. 1989). However, tests based on decreased exocrine function can never be one hundred per cent sensitive in the diagnosis of CP (Dimango 1998). Even some patients with pancreatic calcification, a recognised hallmark of advanced chronic pancreatitis, have normal exocrine function (Lankisch et al. 1986).

Indirect pancreatic function tests

For many years, gastroenterologists have searched for an accurate, simple, easy, sensitive, and specific noninvasive test that can detect mild-to-moderate decreased exocrine function in patients without signs of pancreatic disease on imaging. Such a test would increase the possibility of diagnosing early chronic pancreatitis, as pancreatic function may decrease in pancreatic diseases even before imaging tests become abnormal.

NBT-PABA or bentirimide test. The NBT-PABA test, which is no longer available in several countries of the world, is a simple noninvasive test that requires minimal technical resources and personnel. The patient receives, together with a test meal, synthetic tripeptide, N-benzoyl-L-tyrosyl-p-aminobenzoic acid, which is split in the duodenum by the pancreas-specific chymotrypsin. The released para-aminobenzoic acid (PABA) is rapidly absorbed from the small intestine, partially conjugated by the liver, and finally excreted in the urine. The recovery rate of PABA in a 6-h urinary collection reflects indirectly the amount of intraluminal chymotrypsin (Gyr et al. 1976, Hoek et al. 1981, Lankisch 1982, Toskes 1983) and serves as a measure of exocrine pancreatic function. The possible use of sulfonamides, sulfasalazine, thiazides, and 5-ASA should be discontinued three days before the test, because these drugs interfere with the assay. The reported sensitivity of the NBT-PABA test ranges from 37% to 100%, depending on the severity of the disease, with most studies revealing sensitivity rates between 60% and 90% (Li et al. 1989). Specificity ranges from 70 to 90% against the “gold standard”, the direct intubation test. Falsely abnormal results have been reported to occur in patients with diabetes, liver diseases, renal insufficiency, small bowel diseases with altered absorption, such as coeliac disease, bacterial overgrowth, partial resection of the small intestine and severe diarrhoea (Lang et al. 1981, Niederau & Grendell 1985). However, a more recent study (Meyer et al. 1987) showed that the NBT-PABA test is not affected by
small bowel or liver disease. The lower normal limit of the PABA test is 50% urinary recovery (Lankisch et al. 1986).

Pancreolauryl test. The principle of the test is similar to that of the NBT-PABA test. In this second type of oral pancreatic function test, the patient receives, together with a test meal, fluorescein dilaurate, which is hydrolysed by pancreatic cholesterol esterase to lauric acid and a free water-soluble fluorescein, which is readily absorbed by the gut, conjugated by the liver, released into the circulation, and excreted into the urine. Urine is collected for ten hours and fluorescein is measured spectrophotometrically. Most commonly, serum concentrations are measured, which can be done within several hours, thereby avoiding prolonged collection of urine, and with the same sensitivity and specificity as in urine collection (Lankisch et al. 1986). Compared to the direct test, the sensitivity is almost 80% in advanced disease, but drops to 40% in mild forms. Reported specificity ranges from 46% to 97% (Niederau & Grendell 1985, Scharpe & Lliano 1987).

Fecal chymotrypsin determination. The determination of chymotrypsin in a small random stool sample still remains a useful screening test for exocrine pancreatic insufficiency (Li et al. 1989). The reported sensitivities usually vary from 72% to 90% and specificities from 62% to 90%. False positives may occur in hepatic cirrhosis, partial gastrectomy, coeliac disease, and Crohn’s disease.

Fecal elastase-1. The new noninvasive direct pancreatic function test, fecal elastase-1, has a higher sensitivity than fecal chymotrypsin and a specificity of 96% in the diagnosis of CP (Löser et al. 1996). It has been suggested to represent the tubeless test of choice in CP (Gullo et al. 1999). However, fecal elastase has not turned out to be helpful in detecting mild-to-moderate pancreatic insufficiency (Lankisch et al. 1998).

2.4.3. Endocrine function tests

Oral glucose tolerance test (OGT). OGT is the only endocrine function test recommended for routine diagnosis of diabetes, and it is the only test for diagnosing impaired glucose tolerance. It is both simple and cheap. (Gallwith et al. 1998).

Intravenous glucagon test. The intravenous glucagon test is the only C-peptide-stimulatory test that has been properly evaluated and compared with the response to an ordinary meal. It is used for the determination of β-cell secretory capacity and is highly predictive of insulin dependency in diabetes. Fasting C-peptide values above 0.6 nmol/l indicate sufficient β-cell capacity without a need for insulin substitution (Gallwith et al. 1998).
2.5. Use of aminoterminal propeptide of type III procollagen and laminin in screening for hepatobiliary and pancreatic disorders

The most common extraintestinal manifestations associated with IBD are hepatobiliary diseases, and PSC is the most common form of chronic hepatobiliary disease in patients with either UC (Shepherd et al. 1983) or CD (Rasmussen et al. 1997). Both pancreatitis and pancreatic insufficiency may also occur as extraintestinal manifestations of IBD (Seyrig et al. 1985, Matsumoto et al. 1989, Niemelä et al. 1989, Piontek et al. 1990). The diagnosis of PSC is based on ERC, which is the gold standard, and liver biopsy findings (Wiesner & LaRusso 1980). The severity of PSC may also be assessed by liver biopsy (Ludwig 1989). Both of these diagnostic procedures, however, are invasive and involve a risk of complications. Therefore, it is not advisable to carry out these procedures frequently. In addition, liver histology provides only a static description of the dynamic process of fibrogenesis (Rojkind & Kershenobich 1981). Furthermore, a liver biopsy specimen may not be representative of the whole liver because of local variations in PSC (Olsson et al. 1995). Both PSC and CP are characterized by continuous inflammation and fibrosis, which suggests that measurement of fibrosis markers could facilitate the diagnosis.

2.5.1. Hepatic fibrogenesis

Hepatic fibrogenesis is characterised by increased synthesis and deposition of collagens in the extracellular matrix. Collagens are synthesized intracellularly as procollagen precursors, which contain extension peptides at both the amino and the carboxyl ends of the molecules. These peptides are cleaved off by specific enzymes converting procollagen into collagen (Fessler & Fessler 1978). The serum level of aminoterminal propeptide of type III procollagen (PIIINP) has been proposed as a marker of fibrogenesis, reflecting the rate of type III collagen synthesis, based on the assumption that one molecule of the propeptide is released into the circulation when one molecule of procollagen III is synthesized (Hayasaka & Saisho 1998). The serum concentrations of both laminin and PIIINP also represent not only the synthesis of these macromolecules, but also possibly increased degradation (Niemelä 1994). Serum PIIINP has been proposed as a test for monitoring disease activity and hepatic fibrosis in chronic liver diseases, such as alcoholic liver disease, primary biliary cirrhosis and chronic active hepatitis (Niemelä et al. 1983, Frei et al. 1984, Eriksson & Zettervall 1986, McCullough et al. 1987). In PSC, serum PIIINP may reflect fibrogenesis in the liver (Stassen et al. 1984). Correlations with elevated serum PIIINP and hepatic fibrosis and portal tract inflammation in patients with PSC have also been reported (Mehal et al. 1992). Apart from indicating fibrogenesis, PIIINP may be a useful predictor of histological progression (Stassen et al. 1984). In a recent study of patients with UC, serum PIIINP above 5.0 μg/l was found to suggest the occurrence of concomitant PSC (Leidenius et al. 1997). The median serum PIIINP was 8.9 μg/l in the 16 patients with PSC, being thus much higher than in the UC and normal liver biochemistry group (3.0 μg/l). In patients with UC and a hepatobiliary disorder
other than PSC, the median serum PIIIINP was significantly higher than in patients with UC and normal liver biochemistry.

Several lines of evidence have suggested that hepatic stellate cells (HSCs) are the most important cell type for matrix production in an injured liver (Friedman 1993). Recently, the identification of pancreatic stellate cells (PSCs) and the similarities of these cells to hepatic stellate cells have suggested that PSCs participate in the development of pancreatic fibrosis (Bachem et al. 1998).

### 2.5.2. Pancreatic fibrogenesis

The course of chronic pancreatitis is characterized by a progressive loss of pancreatic parenchyma with replacement by fibrotic tissue (Sarles et al. 1979). The development of these lesions initiates in the ducts, with periductal fibrotic tissue proliferation producing progressive disappearance of the acinus (Nakamura et al. 1972). Pancreatic fibrosis is constituted mainly by collagen types I, III, and IV, procollagen III, and fibronectin, which are localized in the interstitial tissue, while collagen IV, laminin, and fibronectin are found in the basal lamina (Kennedy et al. 1987, Uscanga et al. 1984).

Only a few studies are currently available on PIIIINP and laminin in pancreatic disease. Adler et al. (1990) reported high serum PIIIINP and laminin levels in severe acute pancreatitis. A study by Navarro et al. (1996) recently indicated that serum PIIIINP levels are elevated in patients with chronic pancreatitis, reflecting the severity of pancreatic fibrogenic activity. No relationship between serum PIIIINP levels and pancreatic exocrine function or disease duration was found. Löhr et al. (1991) found increased levels of PIIIINP and laminin in patients with either chronic or acute pancreatitis. Concomitant liver diseases were excluded. The highest levels of laminin were found in patients with an acute episode of chronic pancreatitis. On the contrary, Domínguez-Muñoz et al. (1993) did not find any increase in the circulating concentrations of laminin in patients with alcohol-induced chronic pancreatitis. However, serum PIIIINP levels were abnormally high in 8 (27%) out of 30 patients, and the authors hypothesized that serum PIIIINP concentrations would reflect the activity of the fibrogenetic process within the gland at the time of sampling.

Laminin is one of the main glucoproteins in basement membranes and plays an important role in cellular adhesion, differentiation, and gene expression (Chung 1993). Serum laminin levels increase in processes that result in neosynthesis or destruction of basement membranes, rather than in fibrogenetic processes (Domínguez-Muñoz et al. 1993). Markedly increased serum laminin levels were found in patients with hepatic fibrosis and cirrhosis and correlated positively with the extent of fibrotic transition of the liver, except in cases of alcoholic hepatitis combined with advanced fibrosis and malfunction, which could display normal value of laminin (Kropf et al. 1988).

The usefulness of circulating PIIIINP or laminin as an index of pancreatic injury in pancreatic disease associated with IBD has not been studied.
3. Purpose of the present study

The aim of the present study was to evaluate cross-sectionally the prevalence of pancreatic and hepatobiliary manifestations in a large unselected and representative group of patients with different types of IBD: colitis ulcerosa (CU), Crohn’s disease (CD), and indeterminate colitis (IC) and to correlate the findings with clinical, endoscopic, and histological variables. The more specific aims were:

1. to estimate the prevalence of pancreatic duct abnormalities and exocrine and endocrine pancreatic dysfunction among IBD patients (I);
2. to evaluate the prevalence of hepatobiliary diseases and to estimate the frequency of coexisting cholangiographic and pancreatographic duct abnormalities in all categories of IBD patients (II);
3. to estimate the prevalence of elevated levels of pancreatic enzymes by correlating the levels of pancreatic enzymes with the clinocopathological features of IBD, and to evaluate the potential mechanisms of enzyme elevation (III); and
4. to investigate the serum concentrations of PIIINP and laminin in IBD patients and their relationship with IBD-associated hepatobiliary and pancreatic disorder and to correlate them with clinical, endoscopic, and histologic variables in the different categories of IBD (IV).
4. Patients and methods

4.1. Patients

All the patients with a diagnosis of chronic IBD examined, treated and followed up regularly during the years 1980-91 at the Gastroenterology Unit at the Department of Internal Medicine, University Hospital of Oulu, Oulu, Finland, were identified from the computerized patient files. The study was carried out during the period 1989-1991. The Gastroenterology Unit is the only unit specialized in gastroenterology in an area with a population of approximately 300 000 in northern Finland, and the adult patients with IBD from this area are routinely referred to this unit for gastroenterological endoscopies and consultations. Cases were also traced at units outside the hospital, including the nearby district hospitals and private and general practices. All these IBD patients have been entered in an IBD register. At the end of the year 1988, at the time of the collection of the material, the register consisted of 509 IBD patients.

To collect half of the regional IBD patients, only the patients born in even-numbered years, aged 18-79 years, and with a definite IBD diagnosis were invited to participate (n=250). The exclusion criteria were pregnancy, severe heart failure and malignant disease (n=4).

The diagnosis had been made on the basis of internationally accepted criteria (Lennard-Jones 1989) and using the histological classification criteria described in the section on histological methods. The differential diagnosis between UC and CD was achieved on the basis of endoscopy, histology and clinical features. The distinction was made more by pattern recognition than by one or more specific features (Lennard-Jones 1992). In at least 10% of the cases of non-specific colitis, it is difficult or impossible to distinguish between ulcerative and Crohn´s colitis. The term “indeterminate colitis” was used in these cases. Table 6 summarizes some endoscopic features of the two main IBD types.

Altogether 246 patients were invited, and 237 agreed to participate. None of them were hospitalized. The final study group, a total of 237 patients, consisted of 170 (72%) patients with UC (77 men and 93 women; median age 43 years, range, 18-77), 46 (19%) patients with CD (24 men and 22 women; median age 38 years, range, 19-78) and 21 (9%) patients with indeterminate colitis (IC) (14 men and 7 women; median age 33 years, range, 20-65). The median duration of the disease was 7 years, range, 1-35. The
corresponding figures were 7 years, range 1-35 for patients with UC, 6 years, range 1-21 for patients with CD, and 5 years, range 1-17 for patients with IC. The disease duration of IC was statistically lower than that of UC (p < 0.05).

Table 6. Some endoscopic distinctions between ulcerative colitis and Crohn’s colitis.

<table>
<thead>
<tr>
<th></th>
<th>Ulcerative colitis</th>
<th>Crohn’s colitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mucosal hyperaemia</td>
<td>Diffuse</td>
<td>Patchy</td>
</tr>
<tr>
<td>Mucosal surface</td>
<td>Smooth</td>
<td>Often cobble-stoning</td>
</tr>
<tr>
<td>Ulcers</td>
<td>Only when severe</td>
<td>Discrete aphthous or large</td>
</tr>
<tr>
<td></td>
<td></td>
<td>deep ulcers common</td>
</tr>
<tr>
<td>Narrowing of lumen</td>
<td>Uncommon (smooth)</td>
<td>Common (ulcerated)</td>
</tr>
<tr>
<td>Rectum involved</td>
<td>95%</td>
<td>50%</td>
</tr>
<tr>
<td>Distribution</td>
<td>Continuous</td>
<td>May be patchy</td>
</tr>
</tbody>
</table>

Adapted from Lennard-Jones 1992.

Nine UC patients (5%) had undergone panproctocolectomy and two (1%) colectomy with a preserved rectum. Of the patients with CD, a total of 19 (41%) had been operated on. Ileocaecal resection had been performed on four (9%), right-sided haemicolectomy combined with ileal resection on four (9%), total colectomy with ileal resection on one (2%), and total colectomy on six (13%) patients. Two patients (4%) had undergone partial resection of the small bowel and another two (4%) partial resection of the large bowel. Of the patients with IC, only one (5%) had had an operation, panproctocolectomy. No stricturoplasties had been done. Only two patients showed elevated creatinine values.

In study IV, the patients were the same as in the other studies, but sera for PIIIINP and laminin determination were not available for 15 patients. Thus, the final study group, a total of 222 patients, consisted of 161 (72.5%) patients with UC (76 men and 85 women; median age 43 years, range 18–77), 41 (18.5%) patients with CD (23 men and 18 women; median age, 38 years, range, 19–78), and 20 (9%) patients with indeterminate colitis (IC) (14 men and 6 women; median age 34 years, range, 20–65). When subgroups of patients with hepatobiliary and pancreatic disorder were formed, the analytical results of study I and II were used.

4.2. Methods

4.2.1. Pancreatic screening

The patients were screened for serum and urinary amylases, serum lipase and urinary para-aminobenzoic acid (PABA) excretion. Serum and urinary pancreatic enzymes were prospectively sampled within 1-19 months after the most recent colonoscopy and
compared with the endoscopic and histological findings obtained previously. No use of alcohol was allowed during the 4 days preceding the examination. After an overnight fast, serum and urinary amylases (using a spot collection) were determined by a kinetic method (Boehringer Mannheim, Mannheim, Germany), serum and urinary isoamylases by an isoamylase kit based on cellulose acetate electrophoresis (Helena Laboratories, Beaumont, Texas), and serum lipase by means of a kinetic turbidimetric method (Boehringer Mannheim) (Ojala & Harmoinen 1975). The normal reference intervals for these tests were as follows: serum amylase 70-300 U/l, urinary amylase <1700 U/l, serum pancreatic isoamylase 30-170 U/l, urinary pancreatic isoamylase 75-1240 U/l, and serum lipase <160 U/l. The normal values for amylases have been checked in healthy individuals in a Finnish population (n=92) with about the same smoking and drinking habits as those of our study group.

Exocrine pancreatic function was assessed by determining urinary para-aminobenzoic acid (PABA) excretion in a 6-h collection following oral administration of 1 g of the synthetic peptide N-benzoyl-L-tyrosyl-p-aminobenzoic acid (NBT-PABA) (Lankisch 1982). The lower normal limit of the PABA test is a urinary recovery of 50%, but in order to avoid overdiagnosing, we used a urinary recovery of 40% or more as a normal value. The possible use of sulfonamides, sulphasalazine, thiazides and 5-ASA was discontinued three days before the test, because these drugs interfere with the assay.

4.2.2. Further pancreatic evaluation

A further diagnostic evaluation of pancreatic function and duct morphology was performed only if the patient fulfilled one or more of the following criteria: 1) Significantly decreased urinary PABA excretion, defined as <40%. 2) Significantly elevated serum or/and urinary amylases or serum lipase at examination, defined as more than twice the upper normal limit (UNL). 3) Previously elevated serum or/and urinary amylase or lipase (as in criterion 2).

The patients (n=71) satisfying one or more of these criteria were invited for a 2-day hospital stay. After an overnight fast, transabdominal ultrasonography was performed by one radiologist (S.L.) using a real-time scanner with a 3.5 MHz transducer. Endoscopic retrograde pancreatographies (ERP) were performed by three experienced endoscopists (S.N., J.L., and B.H.) using an Olympus duodenoscope JF 1T10 (see flow chart in Fig 3 on page 45). Biopsy specimens were taken from the descending duodenum, antrum and corpus. If ERP had previously been performed for some reason, it was not repeated.

The pancreatograms were analysed by one radiologist (S.L.) blind to the clinical data. The films were classified according to the generally accepted Cambridge classification (Jones et al. 1988): A normal pancreatogram was defined as one of good quality with completely normal pancreatic duct and side branches. If the main pancreatic duct was normal, but either one or two side branches abnormal, the pancreatogram was defined as equivocal. When three or more side branches were definitely abnormal, the pancreatogram was classified as showing mild changes of chronic pancreatitis. If the main pancreatic duct was abnormal with or without branch changes, the pancreatic changes were considered as moderate. The changes were classified as marked if they showed moderate changes and, in
addition, at least one of the following abnormalities: main duct obstruction, severe irregularity or dilatation, ductal filling defects or a large cavity.

After an overnight fast, before the ERCP, the exocrine function of the pancreas was measured using the secretin test according to the current standardization (Dreiling & Janowitz 1962). A bolus (1 CU/kg body weight) of synthetic secretin (Sekretolin Diagnosticum, Hoechst AG, Frankfurt, Germany) was then injected intravenously. The calculated maximal bicarbonate concentrations were used as indicators of exocrine pancreatic function. In our laboratory, the normal value for maximal bicarbonate concentration was >80 mmol/l and the maximal volume >150 ml (Lehtola et al. 1984). Endocrine pancreatic function (beta cell function) was assessed using the glucagon C-peptide test (Rendell 1983) with a double antibody radioimmunoassay (Diagnostic Products Corporation, Los Angeles). For the glucagon test, the normal C-peptide values were 0.6 - 3.0 μg/l at time 0 and >2.5 μg/l at 6 minutes.

4.2.3. Hepatobiliary screening

The values of serum aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT), alkaline phosphatase (ALP), bilirubin, and albumin were routinely determined and the previous values re-evaluated. Serum values from tests performed in direct connection with other diseases, surgery, or endoscopic procedures were not included.

4.2.4. Further hepatobiliary evaluation

We decided to perform transabdominal ultrasonography, endoscopic retrograde cholangiography (ERC) and liver biopsy only if the patient fulfilled one or more of the following criteria (n=37): 1) aminotransferases (ASAT and/or ALAT) increased to more than twice the UNL. 2) Alkaline phosphatase (ALP) increased to more than 1.5-fold the UNL. 3) Aminotransferases and/or ALP previously (once or more often within 5 years) or constantly increased as described in 1) and 2). Transabdominal ultrasonography and ERC were performed as described in 4.2.2. If the biliary tree was not filled, intravenous cholangiography was performed (n=6). At the time of the investigation, MRI and CT cholangiography were not available. If ERC had previously been done for some reason, it was not repeated (n=4).

The cholangiographic changes were graded as mild (slight, typical irregularities), moderate (one or more stenoses of extrahepatic and intrahepatic bile ducts), and advanced (pronounced stenoses of extrahepatic and central bile ducts and peripheral obliteration of intrahepatic ducts) (Lindström et al. 1990).
4.2.5 Measurements of the markers of connective tissue metabolism

Blood samples for measurements of PIIINP and laminin were prospectively taken at the time of the medical examination, within 1–19 months after the most recent colonoscopy. The serum was separated by centrifugation and stored at −20 °C until analysis. The serum samples were stored for up to 6 months. Serum PIIINP was measured by an equilibrium assay method based on the human antigen, using commercially available reagents (PIIINP RIA; Orion Diagnostica, Oulunsalo, Finland). The reference interval for PIIINP in adults is 1.7–4.2 μg/l. The intra- and interassay coefficients of variation of PIIINP RIA are <5% and <6%, respectively (Risteli et al. 1988). Laminin was measured using a radioimmunoassay (RIA) method described previously (Kropf et al. 1988). UNL, as given by the manufacturer, was 1.6 μg/l.

4.2.6. Formation of subgroups of IBD patients with and without hepatobiliary and/or pancreatic abnormalities

In order to evaluate whether hepatobiliary and pancreatic disorders have a cumulative effect on the concentrations of the fibrotic markers, the following four subgroups were formed: (1) Patients with no signs of hepatobiliary or pancreatic disorder (IBD without complications). (2) Patients with one or more of the following three criteria were classified as having a pancreatic disorder: a) A PABA excretion test <30%, b) pancreatic duct abnormalities in ERP, and c) an abnormally low bicarbonate concentration in the secretin test. (3) Patients with a hepatobiliary disorder (increased liver enzymes) but without a pancreatic disorder were classified as having IBD and a hepatobiliary disorder. (4) Patients with both increased liver enzymes and a pancreatic disorder were classified as having a combined pancreatic and hepatobiliary disorder.

4.3. Medical history of the patients

A detailed history was obtained from the medical records and in a face-to-face interview with each patient within 3 months after the invasive hepatobiliary investigations, and the following data were recorded in a questionnaire: the duration and the time of onset of the disease, age, body mass index (BMI), sex, the severity, endoscopic activity and extent of the disease, previous and current medication and the clinical activity of the disease, current symptoms, surgery, previous and/or concurrent medical conditions, and the duration and quantity of smoking and alcohol intake. The current clinical disease activity was defined as severe if the patient had more than four daily bowel motions containing pus/blood, abdominal pain, and subnormal hemoglobin and elevated C-reactive protein concentrations, as moderate if the patient had the above bowel symptoms without pain and altered laboratory values, and as mild if the IBD symptoms were occasional or absent.
Retrospective clinical activity was considered severe if the patient had had no remission at all, moderate if there had been recurrent relapses more than twice a year, mild if the relapses had been fewer than twice a year, and inactive if the patient had been asymptomatic after an acute onset of the disease. Endoscopic activity was regarded as severe if active colitis (friability, granularity, ulceration, or hemorrhage) was seen at every endoscopy, as moderate when signs of inactive colitis were present at every endoscopy, as mild when endoscopic relapses of colitis occurred at times, and as inactive when the endoscopic findings were normal after the onset of the disease. For an analysis of the relationship between clinical or endoscopic activity and the levels of fibrotic markers, cases showing severe or moderate activity were pooled into one group and those with mild or no activity into another. The median number of endoscopies per patients was 5 (range 1–25) for the whole group.

4.4. Histological evaluation of IBD

Biopsy specimens were taken at all endoscopies and included specimens from both endoscopically affected and unaffected bowel regions, to show the histologically active borders. The endoscopically taken histologic specimens, which were available for 233 (98%) patients, were re-evaluated by one pathologist. The material was fixed in formalin, embedded in paraffin, and stained with haematoxylin and eosin.

Histologic classification and estimation of inflammatory activity was performed with uniform criteria as described previously (Chong et al. 1985, Rutegård et al. 1990). The extent of histological activity was assessed using a five-point scale slightly modified from Rutegård et al. (1990): 0) normal or mucosal atrophy without signs of inflammation; 1) increased lymphocytes; 2) small amounts of neutrophilic leukocytes; 3) moderate amounts of neutrophilic leukocytes and/or crypt abscesses; and 4) ulcerative inflammation, epithelial loss and degeneration, and large amounts of neutrophilic leukocytes. The activity in the most actively inflamed area was recorded.

The extent of histologically active inflammation was also estimated if possible, i.e. if the specimens covered the proximal and distal borders of the inflamed zone. The inflammation was considered active if the activity score was 2 or higher. The total extent of histological inflammation was similarly estimated on the basis of the distribution of any histological features consistent with IBD, whether active or inactive. A cumulative histological activity index for each patient was created by dividing the number of histological examinations showing active inflammation (activity score 2 or greater) with the total number of examinations performed on the patient.

4.5. Ethical consideration

The study was approved by the Ethical Committee of the Medical Faculty, University of Oulu.
4.6. Statistical methods

Continuous data are presented as median and range from the 25th to the 75th quartile (IQR), except for patient age and disease duration, which are expressed as median and range (minimum to maximum). The differences in the median values between two groups were determined by paired or unpaired Student’s t test, as appropriate, and p values of <0.05 were considered significant. Comparisons across several different group means were made by analysis of variance. \( \chi^2 \) analysis was used to assess the distribution of categoric variables within the groups. When necessary, logarithmic or exponential transformation of variables was performed to obtain a normal distribution.
5. Results

5.1. Pancreatic duct abnormalities and pancreatic function in patients with chronic IBD (I)

5.1.1. Primary screening investigation

The whole study group (n=237) was initially screened for increased pancreatic enzymes and decreased urinary PABA excretion. Seventy-one (30%) patients had abnormal pancreatic screening tests and were included in the study for a further pancreatic evaluation (Fig. 2). Most of the patients (70%) were included because of decreased urinary PABA excretion (<40%). There were no differences in this respect between UC and CD patients.

Fig. 2. The distribution (%) of the 237 IBD patients screened for pancreatic enzymes and subjected to a PABA test is shown on the left. The endoscopic retrograde pancreatography (ERP) findings of those with indications for further pancreatic evaluation are shown on the right.
5.1.2. Further pancreatic evaluation

Further pancreatic evaluation consisted of ERP, ultrasonography, and a secretin test.

5.1.2.1. Pancreatographic findings.

Of the 71 patients with indications for further pancreatic evaluation, technically satisfactory pancreatograms were obtained for 59 (Fig. 2). Twenty (34%) of the 59 pancreatograms were abnormal (Table 7). When scheduled for the screening based on decreased PABA and increased pancreatic enzymes, 20 of the 237 (8.4%) patients appeared to have duct abnormalities, the frequency of duct changes being 8.2% for UC, 8.7% for CD and 9.5% for IC. The presence of ductal changes was not associated with endoscopic or histological disease extent, histological activity, levels of pancreatic enzymes, BMI, present and retrospective disease activity, previous and current medication, duration and quantity of alcohol intake, or frequency of surgery. Of the seven IBD patients with a previous history of acute pancreatitis, four showed ductal changes at ERP.

Table 7. Endoscopic retrograde pancreatography (ERP) findings of 59 pancreatograms in 71 inflammatory bowel disease patients (%) with indications for further pancreatic evaluation.

<table>
<thead>
<tr>
<th>ERP findings</th>
<th>UC</th>
<th>CD</th>
<th>IC</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 50 (70)</td>
<td>n = 17 (24)</td>
<td>n = 4 (6)</td>
<td>n = 71 (100)</td>
</tr>
<tr>
<td>Normal</td>
<td>30 (60)</td>
<td>8 (47)</td>
<td>1 (25)</td>
<td>39 (55)</td>
</tr>
<tr>
<td>Abnormal</td>
<td>14 (28)</td>
<td>4 (24)</td>
<td>2 (50)</td>
<td>20 (28)</td>
</tr>
<tr>
<td>Mild</td>
<td>5</td>
<td>1</td>
<td>-</td>
<td>6</td>
</tr>
<tr>
<td>Moderate</td>
<td>9</td>
<td>2</td>
<td>2</td>
<td>13</td>
</tr>
<tr>
<td>Marked</td>
<td>-</td>
<td>1</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Failed</td>
<td>2 (4)</td>
<td>2 (12)</td>
<td>1 (25)</td>
<td>5 (7)</td>
</tr>
<tr>
<td>ERP contraindicated</td>
<td>4 (8)</td>
<td>3 (18)</td>
<td>-</td>
<td>7 (10)</td>
</tr>
</tbody>
</table>

CD = Crohn’s disease; IC = indeterminate colitis; UC = ulcerative colitis.

5.1.2.2. Ultrasound findings

Of the 71 patients with an indication for pancreatic evaluation, eight (11%) had abnormal sonographic findings. Of the 20 patients with pancreatic ductal changes, six (30%) showed abnormal sonographic texture of the pancreas. In one of these, ultrasound and plain film of the abdomen showed calcification of the body of the pancreas, and this patient had marked ductal changes at ERP. In the remaining five, all with moderate ductal
abnormalities, ultrasonography showed increased or patchy echogenicity of the pancreas. Small gallstones were seen in the gallbladder in two (10%) patients, both with mild changes at ERP.

5.1.2.3. Exocrine function

A secretin test was performed on 54 (76%) of the 71 patients with abnormal screening tests. Ten (19%) of the 54 patients had abnormally low maximal bicarbonate concentrations (≤80 mmol/l). Five of the 10 patients with decreased bicarbonate secretion showed unequivocal ductal abnormalities in ERP. The other five patients with low secretin test values had normal pancreatic ducts. Of the 20 patients with ductal changes, 17 underwent the secretin test, and only five (29%) showed decreased pancreatic function.

5.1.2.4. Endocrine function

The mean C-peptide values six minutes after a glucagon injection were significantly lower in the patients (n=10) with an abnormally low bicarbonate concentration (≤80 mmol/l), as were also the mean Δ C-peptide values, compared to the patients (n=42) with a normal bicarbonate output (p <0.05). Three (15%) of the 20 patients with ductal abnormalities were found to have overt diabetes, and they all showed a decreased bicarbonate concentration (≤80 mmol/l) in the secretin test.

5.1.2.5. Crohn’s disease changes in the upper gastrointestinal tract

Eight of the 59 (14%) patients scheduled for ERCP showed histological CD changes (probable or definitive) in biopsies obtained from the upper gastrointestinal tract. Of these eight patients, six underwent ERP and four showed ductal changes.

5.2. Hepatobiliary and concurrent pancreatic duct abnormalities in patients with IBD (II)

5.2.1. Patients with abnormal liver test results

The whole study group (n=237) was initially screened for abnormal liver function in order to justify further evaluation of the prevalence of cholangiographic and histological liver changes. Thirty-seven (15.6%) patients (23 men and 14 women; mean age 42.2±2.1
years, range 23-73) showed pathological test results and were included in the study for a further hepatobiliary evaluation. The inclusion frequency was higher among the patients with CD (30.4%) than among those with UC (11.2%, p <0.05). Most of the patients (70%) were included because of previously elevated aminotransferases and/or ALP values.

237 patients with IBD

37 with indications for hepatobiliary evaluation

71 with indications for pancreatic evaluation

19 with only hepatobiliary indications

18 with both hepatobiliary and pancreatic indications

53 with pancreatic indications only

ERC, i.v. cholangiography

ERC additional to ERP

6 with ductal ERC changes including

2 with concurrent CHPG changes

4 with ductal ERC changes, including

2 with i.v. CHG changes including

3 with concurrent CHPG changes

11 with ductal ERC changes including

6 with concurrent CHPG changes

23 with CHG changes including

11 with concurrent CHPG changes

Fig. 3. Flow chart of cholangiographic and pancreatographic studies in patients with inflammatory bowel disease. For details, see text. CHG = cholangiographic; CHPG = cholangiopancreatographic; ERC = endoscopic retrograde cholangiography; ERP = endoscopic retrograde pancreatography, IBD = inflammatory bowel disease
The patients with abnormal liver tests showed no differences in age, gender, BMI, disease duration, endoscopic or histological disease extent, previous or current medication, duration and quantity of alcohol intake, frequency of surgery and actual and retrospective disease activity as compared to the patients with normal liver function tests.

For the 37 patients, 26 successful endoscopic cholangiograms were obtained. Ten of them showed cholangiographic changes. In six of the 37 patients, the biliary tree did not fill and intravenous cholangiograms were performed. Two of the six showed abnormal cholangiograms. Five patients refused. Altogether 32 cholangiograms were performed, and 12 (37.5%) of them showed cholangiographic changes. Twenty (62.5%) of the 32 cholangiograms were normal (4 i.v. cholangiograms included). In addition, 27 technically satisfactory pancreatograms were obtained when ERCP was done to study bile ducts. Of these, 12 (44%) showed pancreatic ductal abnormalities, five with mild, five with moderate and two with marked changes. Concurrent cholangiographic and pancreatic duct changes were seen in 5 of the 37 (14%) patients with hepatobiliary indications for ERCP (Fig. 3).

Parallel to this study, another group of patients (n=71) were studied with pancreatic indications for ERCP (study I). As a result of this study, we obtained 11 additional pathological cholangiograms, because ERP mostly showed both the pancreatic and the bile ducts to fill simultaneously. The cholangiographic changes were mild and intrahepatic in all patients except one, in whom moderate abnormalities were seen and who showed both extra- and intrahepatic changes. In 6 of these 11 patients with cholangiographic changes, concomitant pancreaticographic changes were also seen. The total frequency of abnormal cholangiograms was 10% (23 of 237), when any indication for ERCP was taken into account. Concurrent pancreatographic and cholangiographic changes were seen in 9% (6 of 71) when ERCP was done for a pancreatic indication (Fig. 3).

5.2.2. Summarized ERCP results in the whole study group

Among the 23 IBD patients with cholangiographic cholangitis changes, 18 had ERP done, and concomitant pancreatic duct changes were seen in 11 instances (11 of 23 = 48%) (Fig. 3, Table 8). Six (55%) of the eleven pancreatograms showed moderate and five (45%) mild duct changes. The prevalence of coexisting cholangiographic and pancreatographic duct abnormalities in the whole study group was 4.6%.

5.2.3. Liver histology

Liver biopsy specimens were obtained from 34 of the 37 patients with laboratory signs of hepatobiliary disease. In six (18%) of the 34 patients the histological findings were consistent with PSC (Table 9). All of these cases showed either proliferation or obliteration or loss of bile ducts, and four additionally showed periductal fibrosis. Stage I features were seen in two cases and stage II changes in four cases (Ludwig 1981). None of
the patients had advanced disease (fibrosis-cirrhosis). Pure fatty changes were seen in eight (24%) patients, but when fatty infiltration with portal fibrosis and portal inflammation was included, the frequency of fatty liver changes was 38% (n=13).

Table 8. Concurrent cholangiographic and pancreaticographic changes in 11 of 23 patients with primary sclerosing cholangitis and inflammatory bowel disease.

<table>
<thead>
<tr>
<th>Cholangiographic grade*</th>
<th>Pancreateographic finding and grade of pancreatitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild 17 (74%)</td>
<td>5 mild</td>
</tr>
<tr>
<td></td>
<td>3 moderate</td>
</tr>
<tr>
<td></td>
<td>5 normal</td>
</tr>
<tr>
<td></td>
<td>4 not done</td>
</tr>
<tr>
<td>Moderate 3 (13%)</td>
<td>2 moderate</td>
</tr>
<tr>
<td></td>
<td>1 not done</td>
</tr>
<tr>
<td>Advanced 3 (13%)</td>
<td>1 moderate</td>
</tr>
<tr>
<td></td>
<td>2 normal</td>
</tr>
<tr>
<td>Total 23 (100%)</td>
<td>11 (48%) concurrent, 7 (30%) normal, 5 (22%) not done</td>
</tr>
</tbody>
</table>

* At endoscopic retrograde cholangiography. In two patients the changes were seen in intravenous cholangiography.

Table 9. Histological changes in liver biopsy specimens from 34 patients with laboratory signs of hepatobiliary disease and inflammatory bowel disease (IBD) in each IBD category.

<table>
<thead>
<tr>
<th>Histological diagnosis</th>
<th>UC (n=17)</th>
<th>CD (n=13)</th>
<th>IC (n=4)</th>
<th>No. of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consistent with PSC</td>
<td>1</td>
<td>3</td>
<td>2</td>
<td>6 (17.7)</td>
</tr>
<tr>
<td>Fatty changes</td>
<td>5</td>
<td>3</td>
<td>-</td>
<td>8 (23.5)</td>
</tr>
<tr>
<td>Fatty changes and portal inflammation</td>
<td>2</td>
<td>-</td>
<td>1</td>
<td>3 (8.8)</td>
</tr>
<tr>
<td>Fatty changes and portal fibrosis</td>
<td>-</td>
<td>2</td>
<td>-</td>
<td>2 (5.9)</td>
</tr>
<tr>
<td>Portal inflammation</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>4 (11.8)</td>
</tr>
<tr>
<td>Mild parenchymal degeneration</td>
<td>1</td>
<td>1</td>
<td>-</td>
<td>2 (5.9)</td>
</tr>
<tr>
<td>Granulomatous inflammation*</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>1 (2.9)</td>
</tr>
<tr>
<td>Haemosiderin accumulation</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>1 (2.9)</td>
</tr>
<tr>
<td>Chronic active hepatitis</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>1 (2.9)</td>
</tr>
<tr>
<td>Normal</td>
<td>4</td>
<td>2</td>
<td>-</td>
<td>6 (17.7)</td>
</tr>
</tbody>
</table>

CD = Crohn’s disease; IC = indeterminate colitis; PSC = primary sclerosing cholangitis; UC = ulcerative colitis; * = patient with sarcoidosis
Table 10. Duct disease classification of 26 patients (%) with primary sclerosing cholangitis (PSC) and inflammatory bowel disease.

<table>
<thead>
<tr>
<th></th>
<th>UC</th>
<th>CD</th>
<th>IC</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small-duct PSC</td>
<td></td>
<td>2</td>
<td>1</td>
<td>3 (11.5)</td>
</tr>
<tr>
<td>Large-duct PSC (intrahepatic)</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>6 (23.1)</td>
</tr>
<tr>
<td>Large-duct PSC (extra- and intrahepatic)</td>
<td></td>
<td>1</td>
<td>1</td>
<td>2 (7.7)</td>
</tr>
<tr>
<td>At least large-duct PSC (intrahepatic)*</td>
<td>8</td>
<td>3</td>
<td></td>
<td>11 (42.3)</td>
</tr>
<tr>
<td>Combined large- and small-duct PSC</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>4 (15.4)</td>
</tr>
<tr>
<td>Total</td>
<td>13(50)</td>
<td>8(31)</td>
<td>5(19)</td>
<td>26 (100)</td>
</tr>
</tbody>
</table>

CD = Crohn’s disease; IC = indeterminate colitis; UC = ulcerative colitis. * Liver biopsy is missing.

5.2.4. Liver histology combined with ERC changes

Table 10 shows the combined results of ERCP and liver histology. Twenty-six patients could be classified as having either small-duct or large-duct PSC, giving a frequency of 11% in the whole study group. Among the patients with PSC, the male/female ratio was 1.36:1. Most of the patients with PSC had substantial colitis. There was no significant difference between the patients with and without PSC with regard to age, disease duration, duration and quantity of alcohol intake, previous and current medication, previous intestinal resection, retrospective and present clinical disease activity, or endoscopic activity. Among the patients with PSC, 13 (50%) showed pancreatic duct abnormalities. Of these thirteen patients, PSC was diagnosed on a histological basis (small-duct disease) in two cases, and on a radiological basis (cholangiography) in the remaining 11.

5.3. Elevated pancreatic enzymes in IBD are associated with extensive disease (III)

Hyperamylasemia was seen in 11% and hyperlipasemia in 7% of the total study group. The corresponding prevalences were 17% and 9% in the patients with CD, 9% and 7% in those with UC (the difference between CD and UC patients was significant for hyperamylasemia, p <0.05) and 10% and 5% in those with IC, respectively.
5.3.1. Disease extent, disease activity, previous bowel resections, and pancreatic enzymes

![Box plots showing serum pancreatic enzyme values expressed as median, 25-75% interquartile range (IQR), 95% range, and outliers in relation to disease extent in patients with IBD. The differences in median values for disease extent in more extensive colonic and ileocolonic disease are statistically significant ($p < 0.05$) compared to the respective values in the rectum and sigmoid colon. $\dagger = p < 0.005$. S-P-isoamylase = serum pancreatic isoamylase.](image-url)
The patients were divided into three groups with regard to endoscopic disease extent: one with disease extent comprising the rectum and the sigmoid colon, another with endoscopically more extensive large bowel disease, and a third with ileocolonic disease. The median values of pancreatic enzymes were found to be highest in those with the most extensive large bowel disease or ileocolonic disease (Fig. 4). There was no difference in the smoking habits or alcohol use between the above mentioned groups.

Serum amylase was higher in the patients with severe and moderate clinical activity evaluated retrospectively than in the patients with mild and inactive disease [204 IU/l (IQR 142–289), n=34, vs 180 IU/l (IQR 145–222), n=203, two-tailed t-test, p <0.05]. The serum pancreatic isoamylase levels were significantly higher in the patients with severe and moderate endoscopic activity, than in the patients with mild and inactive endoscopic findings [100 IU/l (IQR 68–136), n = 88, vs 83 IU/l (IQR 67–110), n=149, two-tailed t-test, p <0.05]. Serum amylase and lipase levels were elevated in the patients with high histologic activity indices (≥0.5) compared to those with low indices (<0.5)(p <0.05 and <0.01, respectively). The thirty-one patients operated on showed higher enzyme levels than those not resected (Table 11). After the exclusion of the patients who had been operated on, statistically significant differences remained between the disease extent and the enzyme levels as described above.

Table 11. Pancreatic enzymes in resected and nonresected IBD patients.

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Operated on (n = 31)</th>
<th>Not operated on (n = 206)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>S-Amylase</td>
<td>206 (163-298)</td>
<td>172 (133-226)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>S-Pancreatic isoamylase</td>
<td>114 (82-154)</td>
<td>88 (66-116)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>U-Amylase</td>
<td>1260 (748-1770)</td>
<td>823 (477-1223)</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>U-Pancreatic isoamylase</td>
<td>788 (363-1078)</td>
<td>490 (286-750)</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>S-Lipase</td>
<td>82 (46-128)</td>
<td>64 (42-98)</td>
<td>NS</td>
</tr>
</tbody>
</table>

The values are expressed as median and 25-75% interquartile range (IQR). NS = not significant.

5.3.2. Group with elevated pancreatic enzymes

One or more of the analyzed enzymes (serum and urinary amylase, serum and urinary pancreatic isoamylase and lipase) were elevated above the UNL in 38 patients (16%). The histologic activity in this group was significantly higher compared to those with normal enzyme levels [0.78 (IQR 0.49–1.0), n=38, vs 0.57 (IQR 0.33–0.94), n=195, two-tailed t-test, p <0.05], and smoking was more common (45% vs 24%, p <0.01). There were no differences in age, disease duration, IBD category, sex distribution, serum triglycerides or
alcohol consumption between the two groups. Ultrasound examinations showed increased or patchy echogenicity of the pancreas in 6 (16%) of the 38 patients.

5.3.3. Smoking and drinking habits and pancreatic enzymes

The smokers had higher median values of urinary amylase and pancreatic isoamylase than the non- and ex-smokers (Table 12). They were also younger and used more alcohol. Because alcohol consumption was more abundant in the smokers than in the non- and ex-smokers, the higher urinary amylases could be partly caused by alcohol. To evaluate the effect of alcohol, two groups were formed. One group (group A) consisted of 20 smokers who were total abstainers. The other group (group B) comprised 75 non- or ex-smokers who were teetotallers. Urinary amylase levels were still significantly higher in group A compared with group B [944 IU/l (IQR 596–1720), n=20, vs 707 (IQR 379–1130), n=75, two-tailed t-test, p <0.05] and could hence be ascribed mainly to smoking.

Table 12. Urinary pancreatic enzyme activities, age, and alcohol consumption in relation to smoking habits in patients with IBD.

<table>
<thead>
<tr>
<th></th>
<th>Smokers (n = 63)</th>
<th>Non- and ex-smokers (n = 174)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>U-Amylase (IU/l)</td>
<td>1100 (629–1170)</td>
<td>804 (426–1200)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>U-Pancreatic isoamylase (IU/l)</td>
<td>678 (392–1015)</td>
<td>471 (260–732)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>37 (31–43)</td>
<td>43 (34–56)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Alcohol consumption (g/wk)</td>
<td>28 (10–60)</td>
<td>9 (0–25)</td>
<td>&lt;0.005</td>
</tr>
</tbody>
</table>

The values are expressed as median and 25–75% interquartile range.

5.3.4. Use of medication and pancreatic enzymes

In the group with elevated pancreatic enzymes consisting of 38 IBD patients, 42% used no medication at all. In the normoenzymic group, the corresponding figure was 29% (p <0.05). There was no correlation between the use of medication (sulfasalazine, 5-ASA, steroids, or a steroid in combination with sulfasalazine or 5-ASA) and any of the pancreatic enzyme activities studied. None of the patients used azathioprine.
5.3.5. Pancreatic enzymes in patients with increased liver enzymes and PSC

All the analyzed amylases were significantly higher in the 15 patients with increased liver enzymes and signs of PSC in ERC or liver biopsy compared to the patients without PSC (Table 13). However, lipase showed no statistical difference. Of these 15 patients, 7 (47%) were in the hyperenzymic group. Of the 15 PSC patients, 6 (40%) had a diagnosis of UC, 6 (40%) were CD patients and 3 (20%) were IC patients. The male-to-female ratio was 1.5. There was no significant difference between the patients with and without PSC with regard to age, disease duration, smoking habits, alcohol intake, current medication or previous intestinal resection. The 37 patients with elevated liver function tests did not, however, show any differences in the median values of serum or urinary amylases, their isoenzymes or lipase as compared to the other IBD patients.

Table 13. Pancreatic enzymes in IBD patients with primary sclerosing cholangitis (PSC) compared to those without PSC.

<table>
<thead>
<tr>
<th>Enzyme (IU/l)</th>
<th>PSC patients (n = 15)</th>
<th>No diagnosed PSC (n = 222)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>S-Amylase</td>
<td>253 (178–363)</td>
<td>178 (144–222)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>S-Pancreatic isoamylase</td>
<td>128 (60–200)</td>
<td>88 (67–115)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>U-Amylase</td>
<td>1380 (776–1995)</td>
<td>840 (492–1270)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>U-Pancreatic isoamylase</td>
<td>831 (307–1355)</td>
<td>502 (302–795)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>S-Lipase</td>
<td>82 (60–112)</td>
<td>69 (45–100)</td>
<td>NS</td>
</tr>
</tbody>
</table>

The values are expressed as median and 25-75% interquartile range. NS = not significant.

5.4. Elevated serum aminoterminal propeptide of type III procollagen (PIIINP) and laminin in IBD indicate hepatobiliary and pancreatic disorders (IV)

5.4.1. Association of the clinical characteristics and markers of connective tissue metabolism

The prevalence of elevated serum PIIINP was 20% in UC, 17% in CD, 15% in IC, and 19% in all IBD patients. The corresponding prevalences of elevated serum laminin were 39%, 46%, 35% and 40%, respectively. Twenty-six (62%) of the patients with increased
laminin values also had elevated PIINP values, and 26 (30%) of those with increased PIINP also had elevated laminin values. One hundred and four (47%) patients showed increased values of either one or both of the markers. Elevated PIINP and laminin showed no relation to gender, BMI, endoscopic or histological disease extent, or duration or quantity of alcohol intake. The relationship between these markers and actual disease activity, histological activity or frequency of bowel resection was not significant, either. However, the patients with severe or moderate retrospective clinical and endoscopic activity showed higher serum PIINP values than those with mild or inactive disease (p <0.05 and p <0.01, respectively).

5.4.2. PIINP and laminin in IBD-associated hepatobiliary disorder

In the 37 patients with elevated liver enzymes [hepatobiliary disorder (HBD) group], both serum PIINP and laminin were significantly increased as compared to the 185 IBD patients with normal liver enzymes [4.50 µg/l (IQR 3.08–5.23), n=37, vs 3.10 µg/l (IQR 2.60–3.70), n=185, p <0.0001 and 1.75 µg/l (IQR 1.50–2.10), n=37, vs 1.45 µg/l (IQR 1.30–1.70), n=185, two-tailed t test, p <0.0001, respectively]. In the HBD group, 18 patients (49%) showed increased PIINP concentrations, whereas laminin was elevated in 22 patients (60%). Both laminin and PIINP were elevated in 13 (35%) of such patients.

5.4.3. PIINP and laminin in PSC

PIINP and laminin concentrations were significantly higher in the patients with elevated liver enzymes and PSC, as confirmed by ERCP or liver biopsy (n=15), than in those with no hepatobiliary disorder (Fig. 5). The patients with elevated liver enzymes without PSC also had higher PIINP and laminin values than those without HBD. Laminin levels were higher in the PSC group than in the HBD group without PSC. All the PSC patients showed increased values of either one or both of the markers compared with an incidence of 41% in the patients with no hepatobiliary disorder (p <0.0001). Thus, serum PIINP had a sensitivity of 73% and a specificity of 85% to detect primary sclerosing cholangitis in IBD patients. The corresponding figures for abnormally high serum laminin were 73% and 63%, respectively.

5.4.4. PIINP and laminin and liver histology

Histological findings of PSC were associated with a significant increase of both PIINP and laminin. Histological fatty changes were associated with increased PIINP concentrations, whereas no increases were seen in laminin values.
Fig 5. Box plots showing serum PIINP and laminin concentrations expressed as median, 25–75% interquartile range (IQR), 95% range, and outliers in IBD patients with elevated liver enzymes and PSC (primary sclerosing cholangitis) and without PSC [hepatobiliary disease (HBD) without PSC] and in IBD patients with normal liver biochemistry (IBD). The median values refer to a comparison with the IBD group. *p <0.005, †p <0.0001.

5.4.5. PIINP and laminin in patients with IBD-associated pancreatic disorder

Both serum PIINP and laminin levels were higher in the patients with abnormal pancreatic screening tests than in those with no pancreatic disorder [3.60 μg/l (IQR 2.70–4.80), n=67, vs 3.10 μg/l (IQR 2.60–3.78), n=155, p <0.01 and 1.65 μg/l (IQR 1.45–2.04) vs 1.45 μg/l (IQR 1.21–1.65), p <0.05, respectively]. Both PIINP and
laminin were elevated in 15 (22%) patients with abnormal pancreatic screening tests as compared to 11 (7%) patients in the group with normal screening values ($p < 0.005$).

Fig. 6. Box plots showing serum PIINP and laminin levels expressed as median, 25-75% interquartile range (IQR), 95% range, and outliers in IBD patients with PABA <30% compared to those with PABA ≥30%. *$p < 0.005$, †$p < 0.0005$.

The patients (n=30) with decreased urinary PABA excretion (cut-off value <30%) showed significantly higher serum PIINP and laminin values than those with more abundant PABA excretion (Fig. 6). This group of 30 patients with low PABA excretion included four patients with PSC. After the exclusion of these 4 patients, statistically significant differences remained for both PIINP ($p < 0.005$) and laminin ($p < 0.05$). Of the patients with low PABA excretion (<30%), 37% had serum PIINP levels above the reference value.
Secretin test was performed on 51 patients in the pancreatic disorder group. Ten patients (20%) had an abnormally low maximal bicarbonate concentration (≤80 mmol/l). Serum PIIINP and laminin values were significantly higher in these ten patients than in those with no pancreatic disease, [4.30 μg/l (IQR 3.40–5.30), n=10, vs 3.10 μg/l (IQR 2.60–3.80), n=171, p <0.01] and 1.80 μg/l (IQR 1.60–2.25, n=10 vs 1.50 μg/l (IQR 1.30–1.74), n=171, p <0.05, respectively]. Five of the ten patients with low bicarbonate concentrations also had PSC.

### 5.4.6. PIIINP and laminin and pancreatic duct changes

ERCP was performed on 59 patients. Twenty showed pancreatic duct abnormalities and 39 had normal ducts. There was no difference in the serum PIIINP values between the patients with and without duct abnormalities and between the patients with duct changes and those with no pancreatic disorder. In contrast, serum laminin values were significantly higher in the patients with duct abnormalities than in those with no pancreatic disorder (Fig. 7). The 20 patients with duct abnormalities included 6 with PSC. After the exclusion of these, the serum laminin values were still higher than in those with no pancreatic disorder, but the difference did not reach statistical significance (p = 0.06).

### 5.4.7. PIIINP and laminin in patients with both hepatobiliary and pancreatic disorders

The effect of combined pancreatic and hepatobiliary disease on serum PIIINP and laminin levels is shown in Fig. 8. The cumulative effect on the PIIINP values is significant. In the 19 patients (8.6%) with both pancreatic and hepatobiliary disorders, both PIIINP and laminin concentrations were significantly higher as compared to those with no organ complications (p <0.0001). The frequencies of elevated PIIINP and laminin in patients with combined pancreatic and hepatobiliary disease were 58% and 69%, respectively. Based on the present data, serum PIIINP has a sensitivity of 63 % and a specificity of 85% to detect hepatobiliary or pancreatic disorder in IBD patients. The corresponding numbers for serum laminin are 69% and 63%.

### 5.4.8. PIIINP and laminin in patients without hepatobiliary or pancreatic disorder

In the patients without hepatobiliary and pancreatic disorders (n=156), the median values of serum PIIINP and laminin did not correlate with the endoscopic or histologic disease extent, disease activity or type of IBD.
Fig. 7. Box plots showing serum PIIINP and laminin concentrations expressed as median, 25–75% interquartile range (IQR), 95% range, and outliers in IBD patients with normal pancreatic ducts, pathological ducts, and no pancreatic disease.
Fig. 8. Box plots with serum PIIINP and laminin concentrations expressed as median, 25–75% interquartile range (IQR), 95% range, and outliers in IBD patients, showing a cumulative effect in relation to increasingly extensive organ complications. PD = pancreatic disorder, HBD = hepatobiliary disease.
6. Discussion

6.1. Study population

The present study is the first assessment of pancreatic and hepatobiliary dysfunction in a large cross-sectional and unselected group of IBD patients, comprising all IBD categories. The final study group, a total of 237 patients, represented about half of the total regional IBD patients and consisted of 170 patients with UC, 46 patients with CD and 21 patients with IC. The catchment area is of a mixed urban-rural type with a population of about 300,000. This gives a calculated prevalence of 113/100,000 for ulcerative colitis and 31/100,000 for Crohn’s disease. These prevalence figures are almost the same as those reported from Copenhagen in 1978 (Binder et al. 1982), somewhat lower than those reported from Copenhagen in 1987 (Langholz et al. 1991, Munkholm et al. 1992) and roughly similar to those previously reported for UC in Finland (Karvonen et al. 1991). The true incidences, however, may be slightly higher because of the possibility of not having all IBD patients registered in the database. The 1:3 ratio for CD and UC found in our study population is the same as has been previously reported for the incidences of these diseases in Finland (Halme et al. 1989, Karvonen et al. 1991), indicating that the study population represents quite well the Finnish IBD patients.

The prevalence of CD in our study was somewhat lower than that reported from Sweden (Lindberg & Järnerot 1991). One explanation is that we paid special attention to the clinical diagnosis of IC, which is a relative new concept and has been disregarded in many studies. If we had disregarded the IC diagnosis, the prevalence of CD might have been higher because of the tendency of IC to later evolve into CD.

We did not find it either reasonable or ethically acceptable to perform invasive tests, such as ERCP, without any signs of pancreatic or hepatobiliary abnormality. Similarly, we did not consider it possible to recruit a control group for these invasive tests with a risk of complications.
6.2. Methods

6.2.1. Original study I

ERP is a tool frequently used in the evaluation of patients with presumed pancreatic disease, and a pancreatogram of adequate quality is essential for interpretation.

What does an abnormal pancreatogram mean? The major diagnostic dilemma occurs when patients with less advanced disease are evaluated prior to the development of calcifications, pancreatic atrophy, or marked dilatation of the pancreatic ducts. In this group, the sensitivity and specificity of ERP were significantly lower than in patients with more advanced disease (Forsmark & Toskes 1995).

At least three kinds of patients could present with abnormal pancreatograms that turn out to be false-positive and not indicative of chronic pancreatitis. First, changes in pancreatic ducts, primarily dilatation of the main duct, have been associated with aging (Kreel et al. 1973), although pancreatic exocrine function is remarkably preserved in aging healthy subjects (Forsmark & Toskes 1995). Our study, however, showed no significant age differences between those with and those without ductal abnormalities. Second, duct changes may be seen after an episode of acute pancreatitis. ERP abnormalities usually resolve within 3 to 6 months, although resolution may occasionally take longer (Forsmark & Toskes 1995). Pancreatic function may also be impaired, although it tends to recover more rapidly than ductographic changes. The frequency of acute pancreatitis in IBD patients has been reported to be 1.4-3.1% (Weber et al. 1993, Tromm et al. 1991). In this study, only seven patients had had one or more episodes of acute pancreatitis, and the period between the episode and ERP was more than a year. Of these seven patients, four had moderate duct changes, which are most likely to represent changes due to chronic pancreatitis. The frequency of idiopathic acute pancreatitis over a follow-up of ten years was 3% in this study. Third, pancreatic duct abnormalities have been reported in nearly half of the patients with gallstone disease (Misra et al. 1990). In the present study, only two of the patients with ductographic changes were shown to have gallstones. The reported sensitivity of ERP for the diagnosis of chronic pancreatitis ranges from 67% to 93%, with reported specificity ranging from 89% to 100% (Forsmark & Toskes 1995). These figures have led the authors of some textbooks to consider ERP the most accurate gold standard for the diagnosis of chronic pancreatitis (Owyang & Levitt 1991). No true gold standard, however, is available for the majority of patients.

It has long been known that a fraction of patients with histologic chronic pancreatitis have normal panimatograms (Cotton 1977). Hayakawa et al. (1992) evaluated the sensitivity of ERP and pancreatic function tests using the “true “ gold standard, i.e. pancreatic histology. In 29 patients with histologically confirmed chronic pancreatitis, sensitivity was 79% for the secretin-cholecystokinin test but only 66% for ERP. The fact that ERP might miss patients with chronic pancreatitis should not be surprising. Inflammatory and fibrotic changes do not occur equally throughout the gland, and parenchymal changes are not necessarily reflected in ductal changes in early disease. Ductal abnormalities may evolve only after a prolonged period of disease (Nagata et al. 1981).

It has recently been questioned whether ERP alone or ERP plus exocrine pancreatic function tests are necessary for diagnosing or excluding chronic pancreatitis or for staging
the disease (Lankisch & Andrén-Sandberg 1993). Both exocrine pancreatic function tests and ERP should be used as complementary diagnostic procedures when chronic pancreatitis is suspected (Lankisch et al. 1996).

What, then, is the gold standard for diagnosing chronic pancreatitis? Ultrasonography-guided or intraoperative confirmation of the diagnosis by histology could be the true gold standard. The correlation between ductal changes and functional impairment is good in patients with marked ductal abnormalities (Bozkurt et al. 1994), but less valuable in patients with minimal changes (Braganza et al. 1982). Our results show that morphological ductal changes occurred more frequently than decreased ductular function. This is consistent with the conclusions drawn by Lindström et al. (1990) that pancreatic damage in patients with IBD and concomitant PSC is primarily confined to alterations of ductal morphology rather than functional impairment. In our study, only 29% of the patients with ductal abnormalities showed a pathological secretin test. This could also be explained by the very small number of patients with marked ductal changes in our patients. On the other hand, five patients with a pathological secretin test had normal pancreatic ducts, suggesting that the secretin test may identify patients with chronic pancreatitis earlier than ERP (Lambiase et al. 1993).

Were all patients with a possible pancreatic abnormality included in the pancreatic evaluation group? Obviously, there are no optimal screening tests available for detecting chronic pancreatitis, and we did not find it either reasonable or ethically acceptable to perform invasive tests, such as ERP, without any signs of pancreatic abnormality. Similarly, we did not consider it possible to recruit a control group for such invasive tests.

The IBD patients were initially screened for increased pancreatic enzymes and decreased urinary PABA excretion. The determination of serum amylase and lipase is generally used to support a diagnosis of pancreatitis. In chronic pancreatitis, the serum enzyme levels may be elevated, normal or low, and in an acute exacerbation of a chronic process, the levels of pancreatic isoamylase and lipase are elevated in about 60% (Ventrucci et al. 1989). In this respect, it must be emphasized that we also used a previous or persistent enzyme increase as an inclusion criterion, thus including patients with a previous or continuous exacerbation process. We used a more than twofold enzyme increase as one screening test for pancreatic abnormality. However, the great majority of patients (70%) were included in the pancreatic evaluation group because of decreased urinary PABA excretion. The NBT-PABA test is an indirect test of pancreatic exocrine function recommended as a screening test, with most studies revealing sensitivity rates between 60% and 90% and specificity rates ranging from 70 to 90% (Li et al. 1989). To prevent overdiagnosis, we applied a lower normal limit of the NBT-PABA excretion test than is commonly used (<40%). Thus, we tried, on the one hand, to include all patients with possible pancreatic abnormality in the pancreatic evaluation group and, on the other, to prevent overdiagnosis both in the screening procedure and in the diagnosis of chronic pancreatitis.

We used the maximal duodenal bicarbonate concentration after secretin stimulation as a direct measure of ductular (fluid, bicarbonate, electrolytes) exocrine pancreatic function. The pancreatic damage in IBD is probably directed against ductular cells. We did not analyse acinar (enzymes) function, which would have required a secretin-cholecystokinin stimulation test. The values reported for the sensitivity and specificity of the secretin test
range from 80% to 90% (Li et al. 1989, Niderau & Grendell 1985). Our data showed a parallel impairment of exocrine and endocrine functions in the patients with chronic pancreatitis, which is in line with the earlier findings (Cavallini et al. 1992).

6.2.2. Original study II-IV

We included patients with and without clinical signs of hepatobiliary disease, but with pathological cholangiograms, into the pancreatic study group. Routine use of ERCP as a screening method for PSC could give even higher frequencies, but is unethical at the present. Similarly, we did not consider it possible to recruit a control group for these invasive tests.

Liver biopsies were only performed on patients with laboratory signs of hepatobiliary disease, and 18% of these patients fulfilled the criteria of PSC. Liver biopsies were not obtained from the 11 patients with cholangiographic changes in the pancreatic evaluation group, but they showed unequivocal bile duct changes and were classified as PSC in spite of their normal liver function tests. PSC may be accompanied by only minor biochemical abnormalities or even normal biochemical tests, including serum alkaline phosphatase (Schrumpf et al. 1988, Balasubramanian et al. 1988).

Large-duct PSC is the classic manifestation of PSC and involves cholangiographically abnormal bile ducts, whereas small-duct PSC involves only microscopically identifiable (interlobular and septal) bile ducts (Wee & Ludwig 1985). Liver biopsies and cholangiograms are thus complementary examinations, and both are needed to establish the extent of the disease (Ludwig 1991).

When estimating the prevalence of elevated pancreatic enzymes in study III, the effects of known factors potentially affecting pancreatic enzyme levels, such as medication and use of alcohol, were taken into account. The possible use of sulphasalazine, 5-ASA, and alcohol was discontinued 3 days before the test.

In study IV, the results of the studies I and II were used to form subgroups, such as hepatobiliary disease, PSC, pancreatic disorder, and liver histology.

6.3. Pancreatic duct abnormalities and pancreatic function in patients with chronic IBD (I)

This cross-sectionally designed study, where selected IBD patients were further examined, showed 4% to have pancreatic exocrine dysfunction and at least 8% to have pancreatic duct abnormalities.

Chronic pancreatitis is a slowly progressive disease with severe exocrine insufficiency sometimes occurring only after 20 years or even longer (Nagata et al. 1981, Ammann et al. 1984, Ammann et al. 1988). As the disease progresses, easily recognizable abnormalities may develop that allow an accurate diagnosis, such as diffuse pancreatic calcifications, marked pancreatic duct dilation, and exocrine and endocrine insufficiency.
Such developments are most common in patients with alcoholic chronic pancreatitis and less common in patients with idiopathic chronic pancreatitis (Ammann et al. 1987). Our series included no heavy drinkers with ductal pancreatitis changes, thus eliminating the most common cause of pancreatitis in the Western societies.

6.3.1. Pathogenesis

It has been hypothesized that UC, PSC and pancreatitis, when seen in combination, are manifestations of autoimmune disease with a genetic disposition (Børkje et al. 1985), leading to “sclerosing cholangitis” of the pancreas (Eisner et al. 1993, Montefusco et al. 1984). The term chronic autoimmune pancreatitis has been suggested for this painless pancreatic affliction (Chari & Singer 1994). Both PSC and idiopathic pancreatitis may precede the onset of clinical IBD. Cases of pancreatitis have earlier been reported in patients with known duodenal CD (Eisner et al. 1993). In our study, four of the eight patients with histological CD changes in the upper gastrointestinal tract showed duct abnormalities. Direct ampullary involvement by the disease may cause intermittent obstruction of pancreatic flow. Granulomatous inflammation of the pancreas was recently described in a patient with CD involving the stomach and the duodenum (Gschwantler et al. 1995). Thus, pancreatic disease seems to be one of the extraintestinal manifestations in all IBD categories, and acute idiopathic pancreatitis may complicate IBD. Pancreatic biopsy would give additional information about the nature of these changes.

6.4. Hepatobiliary and concurrent pancreatic duct abnormalities in patients with IBD (II)

6.4.1. Hepatobiliary disease

The prevalence of patients with laboratory signs of hepatobiliary disease in UC and CD varies considerably. The prevalence rates of UC range from 3% to 17% (Perrett et al. 1971, Dew et al. 1979, Shepherd et al. 1983, Wewer et al. 1991, Broomé et al. 1994), and those of CD from 8% (Lind et al. 1985) to 30% (Wewer et al. 1991). In this study, the overall prevalence among unselected IBD patients was 16%, differing considerably in each IBD category as follows: 11% in UC, 30% in CD and 19% in IC, which figures are in line with the results of another Scandinavian study (Wewer et al. 1991).

6.4.2. Primary sclerosing cholangitis

Most patients with UC showing persistently abnormal liver function are likely to have PSC (Shepherd et al. 1983). Many studies have shown a prevalence of PSC ranging from
2.4% to 7.5% in patients with UC (Olsson et al. 1991, Schrumpf et al. 1980), but the use of different inclusion criteria makes it difficult to compare the prevalence figures in separate studies. Up till now, mostly UC patients have been studied, and only a few studies have attempted to determine the prevalence of PSC in CD, showing prevalence rates of 1.4% to 6.4% (Tobias et al. 1983, McGarity et al. 1991). Aadland et al. (1987) suggested that PSC is equally frequently seen in CD as in UC. In a retrospective study, 8% of IBD-associated PSC patients had CD (Broomé et al. 1996). In a recent study, Rasmussen et al. (1997) reported PSC to be the major hepatic disease in patients with CD and abnormal liver function, with an overall prevalence of 3.4%. The prevalence of PSC in patients with colonic CD was 9%. In the present study, a prevalence of 11% for PSC was recorded in a group of unselected IBD patients. PSC was more common in patients with CD (17.4%) than in patients with UC (7.6%). The prevalence figures are higher than the results of most studies, but lower than the results of Boberg et al. (1994), who found a high prevalence of 29%, clearly due to selection bias, as pointed out by the authors.

The findings show that the patients with UC, CD and IC are similarly predisposed to developing hepatobiliary and pancreatic disease, which, in turn, suggests a common IBD-associated factor as a cause of these extraintestinal manifestations.

The reasons why PSC has been infrequently recognized in patients with CD may include a lack of physicians’ awareness and the possibility that PSC in CD may constitute a milder form of the disease (Rasmussen et al. 1997). Total colonic involvement has been thought to be a prerequisite for PSC (Aadland et al. 1987, Rasmussen et al. 1997). The presence of an epitope shared by colonic and biliary epithelial cells suggests a role for humoral immune abnormalities in the pathogenesis of PSC (Mandal et al. 1994).

6.4.3. Concomitant pancreatic duct changes in hepatobiliary disease

The prevalence of abnormal pancreatograms in patients with PSC has ranged widely from 0 to 77% (Table 14). Thirteen of our 26 PSC patients (50%) had abnormal pancreatograms. The mechanisms causing pancreatic involvement in PSC associated with IBD are not clearly understood. In study I, it turned out that at least 8% of IBD patients have pancreatic duct abnormalities, and the present study supports the view that both PSC and pancreatic changes occur independently during the clinical course of IBD. Abnormal pancreatograms are not unique to PSC. They are even more common in primary biliary cirrhosis (PBC) (Epstein et al. 1982), and 60% of the patients with cholangiocarcinoma have them (Palmer et al. 1984). On the other hand, chronic calcific pancreatitis, which is commonly caused by alcohol abuse, may result in distal common bile duct stenosis (Afroudakis & Kaplowitz 1981). Our series included no heavy drinkers with ductal pancreatitis changes, thus eliminating the most common cause of pancreatitis in Western societies. It is possible that, in some instances, the changes in the pancreatic ducts represent extensions of the same disease process that affects the bile ducts (MacCarty et al. 1983).
Table 14. Frequency of chronic pancreatitis (CP) at endoscopic retrograde pancreatography (ERP) in patients with primary sclerosing cholangitis (PSC) associated with inflammatory bowel disease according to eleven recent series.

<table>
<thead>
<tr>
<th>Reference</th>
<th>UC n</th>
<th>CD n</th>
<th>IC n</th>
<th>PSC n</th>
<th>CP frequency (%)</th>
<th>Abnormal SPT frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epstein, 1982</td>
<td>13</td>
<td></td>
<td>20</td>
<td>3/20 (15)</td>
<td>0/8</td>
<td></td>
</tr>
<tr>
<td>Shepherd, 1983</td>
<td>681</td>
<td>17</td>
<td>5/10 (50)</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MacCarty, 1983</td>
<td>55</td>
<td>2</td>
<td>3/40 (8)</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Palmer, 1984</td>
<td>8</td>
<td></td>
<td>10/13 (77)</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Børkje, 1985</td>
<td>151</td>
<td>7</td>
<td>4/7 (57)</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aadland, 1987</td>
<td>22</td>
<td>3</td>
<td>2</td>
<td>0/27 (0)</td>
<td>0/21</td>
<td></td>
</tr>
<tr>
<td>Jorge, 1988</td>
<td>9</td>
<td>4</td>
<td>30</td>
<td>5/24 (21)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Stockbrügger, 1988</td>
<td>36</td>
<td>2</td>
<td>5</td>
<td>2/34 (6)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Lindström, 1990</td>
<td>12</td>
<td>1</td>
<td>1</td>
<td>4/17 (24)</td>
<td>1/17</td>
<td></td>
</tr>
<tr>
<td>Rasmussen, 1992</td>
<td>305</td>
<td></td>
<td>11</td>
<td>0/10 (0)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Own series, 1997, (Study II)</td>
<td>170</td>
<td>46</td>
<td>21</td>
<td>26</td>
<td>13/26 (50)</td>
<td>7/18</td>
</tr>
</tbody>
</table>

CD = Crohn’s disease; IC = indeterminate colitis; UC = ulcerative colitis; SPT = secretin or secretin-pancreozymin test.

Apart from occurring in patients with PSC, pancreatic involvement has been observed in many autoimmune disorders, such as Sjögren’s syndrome (Lindström et al. 1991), and PBC (Epstein et al. 1982). The pathology of this painless and often asymptomatic pancreas affliction is incompatible with that described in classical chronic pancreatitis, and the term “chronic autoimmune pancreatitis” has therefore been suggested for this form of chronic pancreatitis (Chari & Singer 1994).

The clinical course of PSC is variable, and a median survival time of 17 years since the diagnosis of liver disease has been reported (Aadland et al. 1987). In a recent paper, the estimated survival rate was significantly higher in asymptomatic patients compared with those who had symptoms (Broome et al. 1996). The prognoses of patients with PSC and CD have never been evaluated. It appears that patients with PSC and CD may have a milder disease of the liver than patients with PSC and UC, perhaps because large-duct PSC is less common in patients with CD (Rasmussen et al. 1997). The pancreatic duct changes observed in PSC have been seen to disappear spontaneously (Bastid et al. 1990) or after treatment with ursodeoxycholic acid (Lebovics et al. 1992).

The course of IBD-associated pancreatitis is poorly known, but according to our experience, it is benign with occasional episodes of symptomatic pancreatitis and rare instances of significant pancreatic insufficiency. However, the occurrence and even the possible coexistence of these extraintestinal manifestations should be kept in mind when treating IBD patients. The question remains as to whether these concomitant pancreatic
duct changes in FSC have any relevant clinical or prognostic implications, and follow-up studies are therefore needed.

6.5. Elevated pancreatic enzymes in IBD are associated with extensive disease (III)

In this study, the patients with a more extensive disease than those with only distal involvement (rectum and sigmoid colon) had higher pancreatic enzyme activities. Katz et al. (1988) reported hyperamylasemia without evidence of pancreatitis in 8% of patients with CD. Tromm et al. (1991) found painless hyperamylasemia or hyperlipasemia in 16% of patients with CD and in 21% of patients with UC in a prospective study of selected patients. They found no relation to either the activity and duration of the disease or drug treatment. Nor did they find, in contrast to our results, any relation to disease extent, with the exception of a higher frequency of hyperenzymemia in Crohn’s colitis compared to ileitis or ileocolitis.

The important question is whether the elevation of pancreatic enzymes in serum is caused by direct pancreatic damage with enzyme leakage into the blood stream or by increased gut permeability of intraluminal enzymes. The pancreatic enzyme elevation observed in more extensive or active disease may represent the abnormal passage of pancreatic amylase from the gut lumen to blood due to the increased permeability of the inflamed mucosa, a mechanism earlier proposed in patients with intestinal infarction showing serum amylase elevation (Pieper-Bigelow et al. 1990). However, cases of clinical acute idiopathic pancreatitis and chronic pancreatitis associated with IBD have been repeatedly reported (Niemelä et al. 1989, Lysy & Goldin 1992, Eisner et al. 1993). In addition, decreased activities of both amylase and lipase in duodenal aspirates have been seen to occur in CD, and the lowest enzyme values were recorded in the patients with the most extensive bowel involvement (Hegnhoj et al. 1990). These findings could support the theory that elevated serum levels of pancreatic enzymes are signs of pancreatic damage and reflect increased leakage or shifting of enzymes from the pancreas to the blood pool.

Kidneys account for about 50% of body amylase removal, the rest being metabolized by the liver and the reticuloendothelial system (Pieper-Bigelow et al. 1990). The main cause of hyperamylasemia after cardiac surgery was found to be a decreased rate of excretion into urine rather than pancreatic cellular damage (Paajanen et al. 1997). In the present study, only two patients showed slightly elevated creatinine values.

There are several potential mechanisms for the suggested enzyme leakage from the pancreas. First, the pancreas might be affected in some way directly by the extent of IBD. Recently, granulomatous inflammation of the pancreas was described for the first time in a patient with CD (Gschwantler et al. 1995). Another explanation could be an enzyme increase related to the pancreatic effects of inflammatory mediators and cytokines released from the inflamed gut. A third mechanism might be associated with inflammation of pancreatic ducts. In PSC, Epstein et al. (1982) found elevated serum pancreatic isoamylase levels in 8 (36%) of 22 patients. In this study, about half of the patients with PSC showed hyperamylasemia. Our research group has found that at least 8% of IBD
patients have pancreatic duct abnormalities (study I), and that 50% of PSC patients have pancreaticographic changes (study II). The term “chronic autoimmune pancreatitis” has been suggested for this form of pancreatitis. An immunologic basis as an etiology is supported by the finding of autoantibodies by immunofluorescence on sections of human pancreas in about one third of patients with CD without pancreatitis (Seibold et al. 1991). The mechanisms causing pancreatic involvement in PSC and IBD could involve a combination of pancreatic outflow obstruction and immunologic factors and, in patients without PSC, inflammatory and immunological ones.

The patients operated on showed elevated serum amylase levels compared to those not resected. A transient elevation of serum amylase levels after proctocolectomy has been reported earlier (Sakanoue et al. 1992). In our patients, the time between the operation and the study was from several months to years, indicating that the abnormality in pancreatic enzyme metabolism associated with surgery is persistent. The mechanism is not known, but pancreatic secretion may be stimulated in some way after total removal of the colon. In addition, the need for operative treatment reflects a more severe course of IBD, and the hyperamylassemia could thus be related to a more active and severe course of the disease.

The smokers had elevated urinary amylase values, which were not due to the use of alcohol. Dubick et al. (1987) found smokers to have basal serum amylase levels about twice as high as those of non-smokers and postulated that smoking enhances the responsiveness of the exocrine pancreas to secretin, resulting in increased amylase production.

Drugs rarely cause acute pancreatitis (Lankisch et al. 1995), although several case reports about drug-induced pancreatitis have been published. This complication typically appears within the first few days or weeks after the initiation of therapy, but was recently found to occur after long-term therapy as well (Fernández et al. 1997). Unexpectedly, a greater portion of patients not using any drugs was found in the present hyperenzymic group compared to the normoenzymic one. Consequently, it is not likely that the elevation of pancreatic enzymes is caused by medical therapy of IBD.

The first suggestion of a significant connection between pancreatic inflammation and IBD was reported in 1950 by Ball et al. (1950), who found chronic pancreatitis in 46 (54%) of 86 patients with IBD post mortem, although none had had clinical evidence of pancreatic disease. Since then, an increasing number of cases with both acute and chronic pancreatitis in IBD have been reported (Niemelä et al. 1989, Lysy & Goldin 1992, Eisner et al. 1993). No epidemiological data on the true frequency of acute unexplained pancreatitis in IBD are available, but the frequencies vary in smaller series between 1.2% and 3.1% (Seyrig et al. 1985, Niemelä et al. 1989, Tromm et al. 1991). In a study of patients with CD, the incidence of acute pancreatitis was strikingly higher than in the normal population (1.4 vs 0.007%) over a follow-up period of ten years (Weber et al. 1993). In the present study with a follow-up from 1982 through 1992, the frequency of unexplained acute pancreatitis was 3% in IBD and 4% in CD.

Small gallstones or sludge have been found to be responsible for at least some cases of pancreatitis in IBD (Lee et al. 1992). More than 60% of patients with idiopathic pancreatitis have been reported to have abnormal bile microscopy or “sludge” (Ros et al. 1991, Lee et al. 1992). Other authors have reported recurrence rates of 30% to 70% for acute pancreatitis in patients with biliary “sludge” during a 2- to 3-year follow-up (Lee et al. 1992, Marotta et al. 1996). In the present study, US examinations revealed small
gallstones in only 4 and “sludge” in only 1 of the patients (n=71) with pancreatic indications for ERCP, and without any history of acute pancreatitis.

In chronic pancreatitis, the serum enzyme levels may be elevated, normal or low, but in an acute exacerbation of the chronic process, the levels of pancreatic enzymes are usually high (Ventrucci et al. 1989). As shown in this study and earlier ones, elevated pancreatic enzymes and pancreatic duct abnormalities do occur in IBD patients, especially those with concomitant PSC (study I, study II). It is therefore possible that even slightly elevated levels of pancreatic enzymes may be an early indicator of a significant pancreatic disease in patients with IBD, but this should be further evaluated in longitudinal follow-up studies.

Clinically, pancreatitis may be asymptomatic, but may also mimic the abdominal signs and symptoms of IBD, particularly Crohn’s disease (pain and diarrhoea). The symptoms of pancreatitis, both acute and chronic, may be erroneously ascribed solely to the IBD itself. At least milder pancreatic disease may easily pass undetected if no pancreatic investigations are made. Consequently, increased clinical awareness of possible pancreatic involvement is recommended in the case of patients with IBD.

6.6. Elevated serum aminoterminal propeptide of type III procollagen (PIIINP) and laminin in IBD indicate hepatobiliary and pancreatic disorders (IV)

The present results indicate enhanced concentrations of both PIIINP, an indicator of type III collagen formation, and laminin in IBD patients with hepatobiliary and pancreatic disorders. No relation was found between PIIINP concentrations and the endoscopic or histological extent of the disease. Earlier studies with selected and relatively small groups of IBD patients have shown mostly normal levels of PIIINP in patients with UC without hepatobiliary disease (Leidenius et al. 1997) and in active CD (Kjeldsen et al. 1995). In the present study, however, some of the patients without laboratory signs of hepatobiliary or pancreatic disease had slightly elevated levels of PIIINP and laminin. Most patients with UC and persistently abnormal liver function tests are likely to have PSC (Shepherd et al. 1983). While ERCP is currently the gold standard in the diagnosis of PSC, liver biopsy findings are necessary to support the diagnosis. Since both of these methods are invasive with a risk of complications, other methods for the detection of hepatic involvement have been searched for.

When interpreting the concentrations of markers of connetive tissue metabolism in circulation, the clearance of these proteins should also be considered. Impaired kidney function may affect peptide concentrations (Niemelä 1994). PIIINP is taken up and metabolized by the endothelial cells of the liver. This clearance is a physiological function of the scavenger receptor of liver endothelial cells (Melkko et al. 1994).

Of the present IBD patients with hepatobiliary disease both with and without PSC, 49% and 60%, respectively, had elevated values of serum PIIINP and laminin, and the median values were highest in the patients with PSC. All of our PSC patients showed increased values of either one or both of the fibrosis markers. Elevated serum
concentrations of PIIINP in PSC have earlier been reported (Stassen et al. 1984), and a correlation with PIIINP and hepatic fibrosis and portal tract inflammation has been described (Mehal et al. 1992). Apart from indicating fibrogenesis, PIIINP may also be a useful predictor of histologic progression (Stassen et al. 1984). In a recent study of patients with UC, serum PIIINP above 5.0 µg/l was found to suggest the occurrence of concomitant PSC (Leidenius et al. 1997).

The present work serves as the first demonstration of increased serum laminin in patients with IBD. Previous studies have shown increased serum laminin concentrations in patients with liver disease correlating with the extent of fibrotic transition. Serum laminin level has also been suggested as an indicator of increased portal venous pressure (Wu & Danielsson 1995).

We used only non-invasive liver tests to screen for hepatobiliary disease. It is probable that IBD patients with normal liver enzymes may have histologic abnormalities, such as fatty infiltration (Broome et al. 1990). Structural liver abnormalities may also be present in a proportion of our patients with no laboratory signs of hepatobiliary disease and account, in part, for the elevated values of PIIINP and laminin in these patients.

The present IBD patients with pancreatic exocrine hypofunction showed higher values of serum PIIINP and, interestingly, also serum laminin than the patients with no pancreatic involvement, suggesting that these markers of connective tissue metabolism are also associated with pancreatic affusion. In addition, the patients with radiological pancreatic duct abnormalities had higher serum laminin values than those with no pancreatic disease. Navarro et al. (1996) have previously found elevated levels of PIIINP in patients with chronic alcoholic pancreatitis, which is in line with our present study of patients with IBD-associated pancreatic disease. However, they did not find any relationship between serum PIIINP and pancreatic exocrine function as measured by the PABA test, possibly due to the small number of patients included in the study. It may be suggested that the elevated levels of serum PIIINP and laminin in patients with IBD and pancreatic disease reflect abnormal fibrogenesis in the pancreas, which may, in some patients, lead to pancreatic exocrine hypofunction.

Study II showed that 50% of PSC patients have abnormal pancreatograms, and both PSC and pancreatic changes occur during the clinical course of IBD. In our present material, 9% of the patients showed both pancreatic and hepatobiliary abnormalities. The highest PIIINP and laminin concentrations were seen in this group. This finding indicates that PIIINP and laminin concentrations reflect cumulatively the associated organ changes in IBD.

Endoscopic and clinical activity of IBD showed weak correlations with PIIINP and laminin, but the other characteristics of bowel inflammation, such as histological activity or disease extent, did not show any significant association with these markers. This is somewhat unexpected, as both synthesis and degradation of connective tissue have been observed in mucosal inflammation of IBD (Graham et al. 1988, Matthes et al. 1993). The weak correlation with mucosal inflammation may be related to several factors. The powerful effect of hepatobiliary and pancreatic changes on the connective tissue markers may cover the possibly minor contribution of mucosal inflammation. Hepatobiliary and pancreatic affusion in IBD is usually associated with more extensive colitis (study III), and this may further conceal the independent effect of mucosal inflammation.
6.7. Clinical implications

According to the present data, pancreatic disease seems to be one of the extraintestinal manifestations in IBD patients, especially in patients with concomitant PSC. Increased awareness of possible pancreatic disease in IBD patients is recommended.

Previously, PSC has been mainly associated with UC, but the present results support the view that PSC is at least equally common in patients with CD. The question remains as to whether the concomitant pancreatic duct changes in PSC have any relevant clinical prognostic implication. The determination of pancreatic enzymes could give some hints as to whether the IBD patient is suffering from an extensive or acute bowel disease, or from a complication, such as PSC. Both seromarkers of fibrosis, PIIINP and laminin, are increased in IBD patients, and not only in patients with hepatobiliary disease and PSC, but also in patients with pancreatic disease. Further follow-up studies are needed to clarify the clinical and prognostic significance of such measurements.
7. Conclusions

1. Pancreatic duct abnormalities and pancreatic exocrine and endocrine dysfunction occur in some patients with IBD, and acute idiopathic pancreatitis may complicate IBD. Pancreatic disease seems to be one of the concomitant extraintestinal manifestations in all IBD categories.

2. Hepatobiliary diseases are at least equally common in patients with UC and CD. The prevalence of PSC in IBD patients, especially in CD, was higher here than has been previously reported, and about half of the PSC patients have concomitant pancreatic duct changes. Coexisting cholangiographic and pancreatographic duct abnormalities in patients with IBD are thus relatively frequent.

3. Pancreatic enzymes are elevated in a significant proportion of patients with IBD, and the enzyme increase is associated with a more extensive and active disease and, in some cases, with PSC. Medication had no influence on the enzyme increase.

4. PIINP and laminin, considered by many as seromarkers of fibrosis, are only moderately elevated in IBD patients, but more clearly elevated in patients with hepatobiliary disease and PSC and in patients with pancreatic dysfunction. There were no relationships between elevated seromarkers and the IBD category, endoscopic or histological disease extent, frequency of bowel resection or actual clinical activity. Despite the statistically significant differences between groups, PIINP and laminin do not differentiate patients well enough for clinical purpose. Nevertheless, monitoring of these concentrations may possibly yield useful information during patient follow-up, and further follow-up studies are therefore needed.
8. References


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