This thesis addresses studies concerning acute and chronic inflammation of the pancreas. The first part of the thesis contains studies regarding the diagnosis, treatment and incidence of acute biliary pancreatitis and azathioprine induced acute pancreatitis. The second part concerns the influence of obesity and smoking on the clinical course of pancreatitis and morphological aspects on the pancreas.

**Part 1 Biliary and drug induced pancreatitis**

In **(chapter 1)** an update is given concerning the etiology and diagnosis of acute biliary pancreatitis. Establishing a biliary etiology in acute pancreatitis is clinically important because of the potential need for invasive treatment, such as endoscopic retrograde cholangiopancreatography (ERCP) or a subsequent laparoscopic cholecystectomy. The etiology of acute biliary pancreatitis (ABP) is multifactorial and complex. A diagnosis of a biliary etiology in acute pancreatitis is supported by both laboratory and imaging investigations. An increased serum level of alanine aminotransferase (>1.0 μkat/l) is associated with a high probability of gallstone pancreatitis (positive predictive value 80–90%). Confirmation of choledocholithiasis is most accurately obtained using endoscopic ultrasonography or magnetic resonance cholangiopancreatography.

In **(chapter 2)** an evaluation of the treatment of acute biliary pancreatitis is given. A systematic review of previous meta-analyses and guidelines on ERCP in ABP was performed. There is consensus in both the meta-analyses and guidelines that ERCP is indicated in case of ABP with coexistent cholangitis and/or persistent cholestasis. By exception of the first meta-analysis, all included studies agreed that there is no place for early ERCP in predicted mild ABP. Consensus is lacking regarding the role of early ERCP in predicted severe ABP as 3 of the 8 meta-analysis and 1 of the 11 guidelines do not advice this strategy. Routine early ERCP in predicted severe ABP is recommend in 6 of the 11 guidelines. Indication of an endoscopic sphincterotomy is not well defined in meta-analyses and guidelines.

In the light of the somewhat confusing and in part conflicting recommendations found in **(chapter 2)** we investigated the opinion and attitude of Dutch gastroenterologists toward the application of (early) ERCP in the clinical management of ABP by means of a nationwide survey **(chapter 3)**. In this survey, the vast majority of Dutch gastroenterologists attest to a role for ERCP in ABP, but indications when to perform ERCP, its timing, and the application of ES vary greatly and are not always in line with the Dutch or other published national guidelines. The results of this survey highlight the need for additional comparative randomized studies to define the role of (early) ERCP in ABP.
Chapter 4 addresses the different treatment options for preventing recurrent attacks of acute biliary pancreatitis (RABP) including conservative treatment, cholecystectomy, ES, and combinations of these options. From the observational literature data it can be concluded that ES is as effective in reducing RABP as cholecystectomy but inferior in reducing mortality and overall morbidity. The combination of ES and cholecystectomy seems superior to either of the treatment methods alone. A prospective randomized clinical trial comparing ES plus cholecystectomy with cholecystectomy alone is needed.

In chapter 5 the cumulative incidence and patient characteristics of thiopurine-induced acute pancreatitis in IBD patients is evaluated. Several reports suggest an increased rate of adverse reactions to azathioprine in patients with Crohn’s disease. The cumulative incidence of thiopurine-induced acute pancreatitis in Crohn’s disease equaled that of ulcerative colitis (UC) (2.6% vs. 3.7%) and this did not differ from vasculitis patients (2.6% vs.1.9%). In the IBD group, 100% of thiopurine-induced acute pancreatitis patients were women, whereas in the vasculitis group the two observed thiopurine induced acute pancreatitis cases (n = 2 of 2) concerned were men (P = 0.012). In this study, the alleged higher cumulative incidence of thiopurine induced acute pancreatitis in Crohn’s disease compared with vasculitis or UC patients was not confirmed.

Part 2 Clinico-morphological studies on pancreatic lipomatosis and pancreatic inflammation

Obesity and insulin resistance cause fatty infiltration of many organs, including the pancreas (pancreatic steatosis [PS]) and the liver (nonalcoholic fatty liver disease [NAFLD]). In chapter 6 we observed a relation between interlobular and total pancreatic fat with the NAFLD activity score, in patients without steatogenic medication. When corrected for body mass index (BMI), no relation could be found. Total pancreatic fat was a significant predictor for the presence of NAFLD but not for NASH. Presence of intralobular pancreatic fat was related to nonalcoholic steatohepatitis (NASH). This chapter demonstrates a relationship between NAFLD and PS, and, intralobular pancreatic fat and NASH. This relationships seem to be mediated by general obesity. The clinical significance of pancreatic steatosis is reviewed in chapter 7. Multiple definitions, clinical associations and synonyms for pancreatic steatosis are described in the literature and can be confusing. In the past, pancreatic steatosis was considered an innocuous condition, a bystander of many underlying diseases (such as congenital syndromes, hemochromatosis and viral infection). However, evidence that pancreatic steatosis (strongly associated with obesity and the metabolic syndrome) has a role in type 2 diabetes mellitus, pancreatic exocrine dysfunction,
acute pancreatitis, pancreatic cancer and the formation of pancreatic fistula after pancreatic surgery is emerging.

In (chapter 8) the relation between (central) obesity and predicted severe acute pancreatitis is studied. Via a post-hoc analysis of an observational, multicenter study we included patients with a primary episode of predicted severe acute pancreatitis from a larger cohort of patients enrolled in a previous randomized clinical trial. Multivariable analysis showed an association between mortality and high waist circumference (WC)/BMI (OR 10.0, 95% C.I. 1.89-52.7), and a lower BMI (OR 0.84, 95% C.I. 0.71-0.99). For morbidity, multivariable analysis showed an association with a higher WC/BMI (OR 11.5 95% C.I. 2.07-63.8) and CTSI (OR 9.81, 95% C.I.: 3.22-29.2) and a lower BMI (OR 0.79, 95% C.I.: 0.66-0.94). With regard to ICU duration of stay, univariable analysis revealed an association between the CTSI (p<0.0001), ventral-dorsal umbilical waist diameter (p<0.0001) and the WC corrected for BMI (p=0.003). This is the first study to show that the "obesity paradox" also exists in patients with predicted severe pancreatitis. Mortality in obese patients with predicted severe pancreatitis is only higher as compared to non-obese patients when they suffer from central overweight. Whereas mortality in obese patients without central overweight is lower.

In (chapter 9) we investigate the effect of tobacco smoking on pancreatic inflammation and fibrosis. Smokers are at risk for pancreatic cancer (PC) and other pancreatic diseases. Cigarette smoking also aggravates the risk of PC in patients with hereditary and chronic pancreatitis (CP) and results in a higher incidence of acute pancreatitis and relapses in CP. Both PC and CP are characterized by a progressive fibrosis. In this retrospective study, we aimed to confirm a relationship between cigarette smoking and pancreatic fibrosis (PF) in humans, via pancreatic tissue acquired during autopsy. PF was scored by assessing severity of intralobular, extralobular, and total PF: grade 0 (normal or mild; 0-25% PF), grade 1 (moderate; 25-50% PF), and grade 2 (severe; >50%). Grade 2-3 total PF and intralobular PF was significantly more present in smokers vs. "never-smokers" (total: 42.9 vs. 26.5%, P=0.027 and intralobular: 39.3 vs. 15.6%, P=0.013), whereas no differences could be found between never-smokers and ex-smokers and between ex-smokers and smokers.

**FUTURE PERSPECTIVES**

**Acute biliary pancreatitis and drug induced pancreatitis**

The role of an early ERCP in the treatment of predicted severe acute biliary pancreatitis will be investigated in the new APEC-trial (Acute Biliary Pancreatitis; early ERC/ES versus conservative treatment), that will start in the end of 2012. This trial will be coordinated by the Dutch Pancreatitis Study Group. In the RABP-study
(a follow-up study of the APEC: Recurrent Acute Biliary Pancreatitis Study) the rates of recurrent acute biliary pancreatitis and other biliary events will be studied in the cholecystectomy versus cholecystectomy /ES versus ES group (patients unfit for surgery). The outcome of this study will bring about the need of an updated biliary pancreatitis guideline. (New) Guideline adherence can be tested in the future via an questionnaire.

The literature on drug induced pancreatitis is scarce. Thiopurine induced pancreatitis seems to be an idiosyncratic reaction. However, after an e-mail correspondence with Professor Sachar (Mount Sanai Medical Center, New York), a dose dependent relationship seems to exist. He described a young male patient with Crohn disease (CD), who developed thiopurine induced pancreatitis after increasing the dosage of 6-MP. Re-challenge resulted in the same clinical picture. Additionally, in my IBD-praxis, I observed a similar case (young male, CD, acute pancreatitis after dose increase of 6-MP). Further investigation, in terms of genetic susceptibility, interval between drug initiation and development of pancreatitis and the presence or absence of thiopurine induced pancreatitis in 6-TG users will give us a more detailed picture of this disease.

**Clinico-morphological studies on pancreatic lipomatosis and pancreatic inflammation**

Pancreatic steatosis is a relatively new clinical entity. Little is known about its pancreatic distribution. A radiological and pathological study would give an insight in this topic or further studies. Normal value’s of pancreatic steatosis and its relation to other syndromes and diseases are barley known. Case finding studies would be very welcome to define the quantity of steatosis in relation to certain diseases. The role of abdominal fat in relation to survival and morbidity in acute pancreatitis is getting clearer. However, more research in terms of fat-distribution, nutritional status, smoking behavior in relation to morbidity and mortality in acute pancreatitis is need. The role of smoking and pancreatic diseases is clearly underlined in the last years. However, exact mechanism of inflammation, fibrosis (pancreatic stellate cell activation) genetic susceptibility and its clinical consequences, such as: pancreatic insufficiency, operative outcome (after Whipple: peri-operative and long term morbidity and mortality), are unknown.