# THE SECRETIN-CCK TEST

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TO WINNY, MANUEL AND DEBORAH

because

Bwami bwa ciluli mbwaanda'

(The riches of the roof are the walls)

# THE SECRETIN-CCK TEST

An evaluation of the clinical relevance of an exocrine pancreatic function test in the diagnosis of nonacute pancreatic disease and an analysis of its relationship with morphological data in chronic pancreatitis.

Een evaluatie van de klinische betekenis van een exocriene pancreasfunctie test voor de diagnostiek van niet-acute pancreasaandoeningen en een onderzoek naar het verband tussen functie en structuur bij chronische pancreatitis.

H.A.HEIJ

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III. GENERAL DISCUSSION

# INTRODUCTION

The secretin cholecystokinin (S-CCK) test has been used in the diagnosis of nonacute pancreatic disease for many years (Burton, Evans et al, 1960). Because the basal pancreatic secretion is relatively small and highly variable (DiMagno & Go, 1982), stimulation, for instance with exogenous secretin and cholecystokinin, is necessary to obtain sufficient quantities of pancreatic juice from the duodenal lumen for analysis. Impairment of pancreatic exocrine function, measured in this way, has been demonstrated in diseases like chronic pancreatitis and tumor of the pancreas (DiMagno, 1982).

The relatively hidden position of the pancreas prompted clinicians to rely on exocrine function tests for many years. Recently, the introduction of imaging techniques like ultrasound computer scan, endoscopic retrograde cholangiopancreatography (E.R.C.P.) and selective angiography of the abdominal vessels, have made the pancreas much more accessible for diagnostic purposes. Furthermore, several noninvasive tests of exocrine pancreatic function have been developed such as the Para Amino Benzoic Acid (P.A.B.A.) test (Arvanitakis, 1976). These developments might be anticipated to cause the 'classical' S-CCK test to become outmoded and lose its clinical value for the diagnosis of pancreatic disease.

However, it has become evident that the newer diagnostic modalities also have their limitations, leaving a blind area in the diagnosis especially of early chronic pancreatitis, where pancreatic function tests may provide important clues (Toskes, 1982[a]). A rising incidence of both chronic pancreatitis (Andersen, Pedersen et al 1982; Hoogendoorn 1978, 1983) and pancreatic cancer (Braganza & Howat, 1979; Kupchik, Reisfeld & Go, 1982) in Western Europe and the USA underlines the importance of adequate diagnostic methods. The poor prognosis of pancreatic cancer, the 'dismal disease', with a 5% 5-year survival rate, is due to the fact that at present only 10% of the patients have potentially curable disease at the time of diagnosis. Early diagnosis may improve survival rate in pancreatic cancer (Morgan & Wormsley, 1977; Moossa, 1982). Thus far, the new diagnostic aids have failed to improve the detection rate of pancreatic cancer(Savarino, Mansi et al, 1983). It is clear that there is still room for improvement in the diagnosis of chronic pancreatitis an pancreatic cancer in spite of the introduction of newmethods.

Therefore, we have evaluated the results of S-CCK testing performed in 300 patients between 1975 and 1982 and compared these with the data provided by the imaging techniques mentioned before to find out whether it is still worthwile to perform the S-CCK test nowadays. That is the main issue of this study.

To that purpose we first analysed the results by discriminant analysis, which serves to select variables by which to distinguish between normal and abnormal test results. Subsequently, the diagnostic performance of the test (sensitivity, specificity, accuracy) was assessed and compared with that of other procedures, particularly E.R.C.P., and with data from the literature. Thus it was possible to assess the value of the S-CCK test and also to construct a rational program for the investigation of patients suspected to have nonacute pancreatic disease.

During the analysis of the S-CCK test results, we became aware of the fact that very little is known about the relationship between functional impairment and structural changes in chronic pancreatitis. In other words, it is not known in which way and to what extent the S-CCK test represents morphological abnormalities of the pancreas. Therefore, we have compared the data of the S-CCK test also with histological findings in a group of patients with chronic pancreatitis.

In the first part of the thesis the relevant literature will be reviewed. After presentation and evaluation of the results of the present study, a general discussion is presented which centers around four issues:

1. what is the role of the S-CCK test in the diagnosis of nonacute pancreatic disease?
2. how does the S-CCK test compare with various other diagnostic modalities, particularly E.R.C.P.?
3. what is the relationship between exocrine functional impairment and structural changes in chronic pancreatitis?
4. is it possible to construct a rational program of diagnostic procedures for the investigation of patients suspected to have nonacute pancreatic disease?

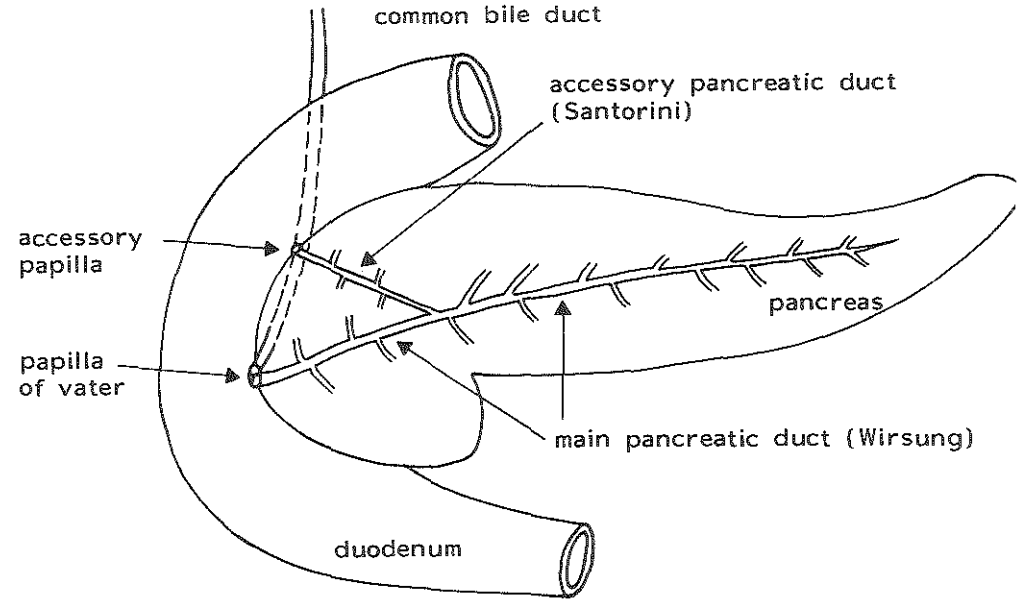



Fig. I.1. Normal anatomy of the pancreatic duct system

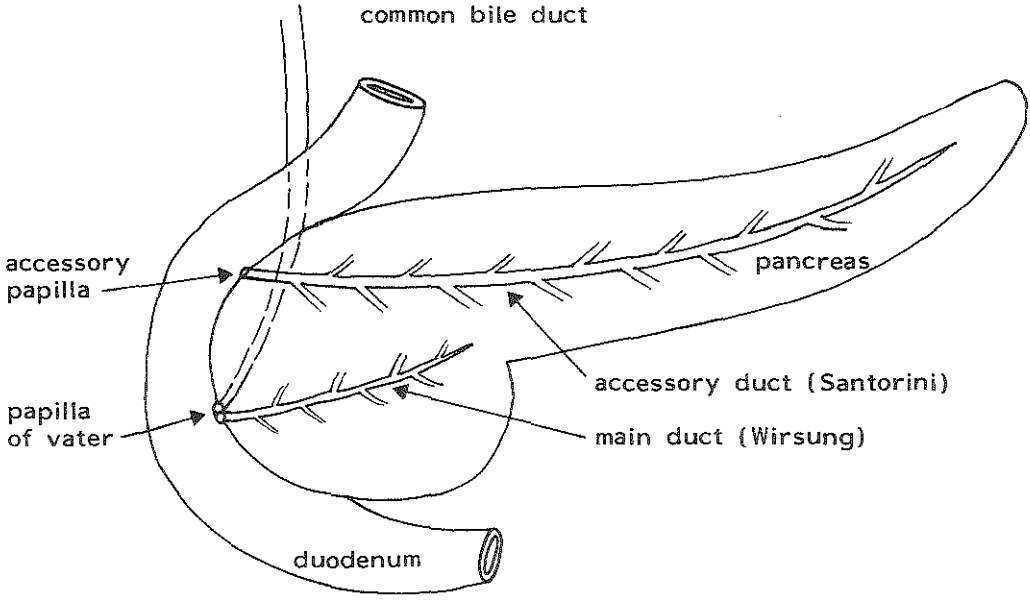



Fig. I.2. Anatomy of the pancreatic duct system in pancreas divisum

# I. REVIEW OF THE LITERATURE.

"...and the most wonderful thing is, that it is written in a book: you cannot say anything against it..."

Multatuli, Idea 391

## I.1 THE PANCREAS IN HEALTH.

The pancreas has been subject of investigation since the discovery of its main duct by Wirsung in 1641. Reinier de Graaf performed the first cannulation of the pancreatic duct, in a dog, in 1665 and analysed the pancreatic juice. He also reported on finding pancreatic stones at autopsy of a melancholical French nobleman who died with bloody diarrhoea (Lindeboom, 1973). In the 19th century, Claude Bernard studied the function of the pancreas in the digestion of food. Later, Pavlov described the neural regulation of pancreatic secretion while Bayliss and Starling discovered the first known hormone, secretin, in 1902. The body of knowledge on exocrine pancreatic function increased in the following decades. In the 1960's Palade and coworkers studied the intracellular processes of the acinar cells (Jamieson & Palade, 1967[a,b]). Although many aspects of pancreatic function and its relation to morphology remain unelucidated, an attempt will be made in this section to outline normal structure and function in order to make subsequent chapters understandable.

### I.1.1 Anatomy

The pancreas develops in embryonic life in a dorsal and a ventral 'Anlage' in close relation to the duodenum. Because of rotation of the foregut both 'Anlagen' fuse and drain their juice via the ventral or Wirsung's duct into the duodenum. (McLean, 1979). The duct of the dorsal part, called Santorini's or accessory duct, has a separate opening into the duodenum in half of the people. Communication between the main duct and the accessory duct exists in 70-90% of the cases (Harris, 1979). See also figures I.1 and I.2

Nonfusion of the ventral and dorsal parts, or pancreas divisum, has been found in 2-10% and might be related to the development of pancreatic pathology (Richter, Schapiro et al, 1981; Thompson, Williamson & Salmon, 1981; Cooperman, Ferrara et al, 1982; Sahel, Cros et al, 1982; Sahel, Boustière et al, 1983).

The adult pancreas has a length of 15 to 25 cm. and weighs about 90 grams. It is located retroperitoneally at the level of the first and second lumbar vertebrae. Three parts are

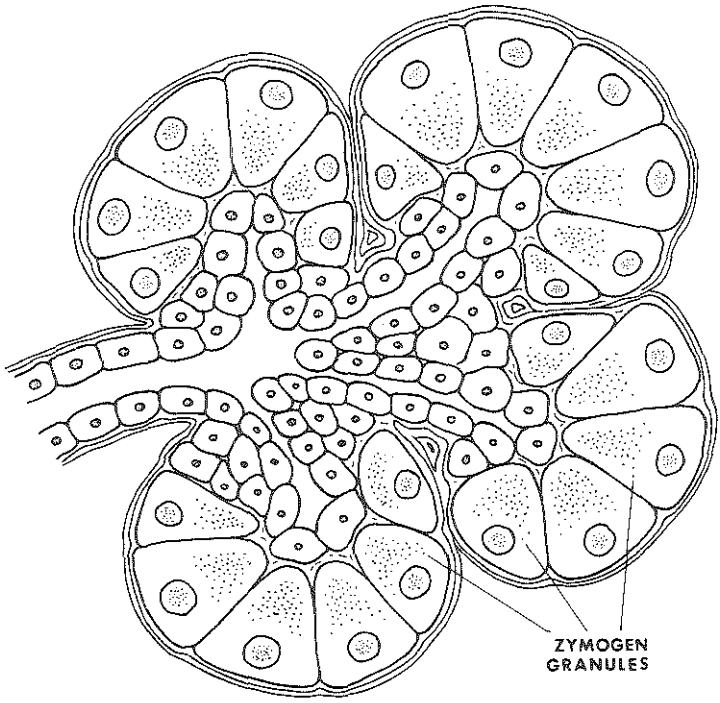



Figure I.3 Schematic representation of 4 pancreatic acini and their relation to an intercalated duct with centroacinar cells at the junction.
(From: R.E.Herman: Manual of Surgery of the Gallbladder, Bile Ducts and Exocrine Pancreas (1979). With kind permission of Springer Verlag, New York).

usually discerned: head, body and tail. The close relation of the gland to neighbouring organs like stomach, duodenum, common bile duct and spleen is of importance in diagnosis and treatment of pancreatic disease. The gland is built along the centrally located main duct which runs the whole length of the organ and into which the side branches drain. The diameter of the main duct averages 4 mm. in the head, 3-4 mm. in the body and 2-3 mm. in the tail (Anacker, Weiss et al, 1977; Stolte, 1979).

The microscopic anatomy of the pancreas has been outlined schematically in Figure I.3. The acini consist of pyramid shaped cells that synthesise proteins and release them into the lumen they surround. At the junction of acini and intercalated ductuli are the centroacinar cells that play an important role in the secretion of water and electrolytes. Groups of acini form a pancreatic lobule that is drained by a intralobular ductule. These intralobular ductuli merge into the interlobular ductuli that run in the fibrous tissue between the lobuli towards the

main pancreatic duct. It should be noted here that this traditional concept of microscopical anatomy of the pancreas has recently been questioned by Bockman and coworkers, who suggest that the acinar cells are not arranged like a bunch of grapes but rather as tubular complexes that form many anastomoses with each other (Bockman, Boydston and Parsa, 1983). The endocrine tissue is mainly located in the islets of Langerhans which are dispersed between the exocrine tissue. The highest concentration of islets is in the tail. The endocrine cells produce several hormones including insulin, glucagon, somatostatin, vasoactive intestinal peptide (V.I.P.) and human pancreatic polypeptide (H.P.P.).

The pancreas derives its arterial blood supply both from the coeliac and from the superior mesenteric artery. Branches from both main trunks form the anterior and posterior pancreatic arcade around the head of the gland. Variations in the anatomy of the arterial supply occur not infrequently and necessitate arteriography prior to major pancreatic resections (Anson & McVay, 1971; Thompson, Eckhauser et al, 1981).

Both sympathetic and parasympathetic nerve fibers, each with afferent and efferent communications, innervate the pancreas. From the sympathetic chain fibers run via the coeliac and superior mesenteric ganglion to the gland parallel to the arteries. The parasympathetic fibers are contained in the vagal nerve. The pancreas itself contains numerous ganglia (Harris, 1979).

## I.1.2 Physiology

### I.1.2.1 Composition of pancreatic juice.

The product of the exocrine pancreas is a clear, watery fluid, rich in electrolytes and proteins, that will be referred to as pancreatic juice. The process of synthesis and transport of proteins and electrolytes will be called secretion subsequently. The average daily volume of pancreatic juice is 1-2 l., but after maximal exogenous stimulation the flow rate may amount to 200 ml. per 30 min. with a bicarbonate concentration 5 times as high as that of the blood (Wormsley, 1969[b]). The concentration of bicarbonate increases with the flow rate while the sum of the concentrations of the anions (bicarbonate and chloride) remains constant and equal to the sum of the cation concentrations (sodium, potassium, calcium and magnesium) (Hermon-Taylor, 1972; Harper & Scratcherd, 1979). The site of the secretion of water and electrolytes, which is also called the hydraletic response, is the epithelium of the ductuli and the centroacinar cells (Fölsch & Creutzfeldt, 1977; Schulz, 1980).

Table I.1 Composition of pancreatic juice (according to Desnuelle & Figarella, 1979; Scheele, Bartelt et al, 1981).

| HYDRALETIC RESPONSE | | | |
|---|---|---|---|
| Anions: | bicarbonate<br>chloride | Cations: | sodium<br>potassium<br>magnesium<br>calcium<br>zinc |

| ECBOLIC RESPONSE | | |
|---|---|---|
| Proteolytic enzymes: | endopeptidases: | trypsinogen<br>chymotrypsinogen<br>pro-elastase |
| | exopeptidases: | procarboxypeptidase A<br>procarboxypeptidase B |
| Lipolytic enzymes: | | lipase<br>colipase<br>phospholipase A2<br>carboxyl ester hydrolase |
| Alpha amylase | | |
| Nucleolytic enzymes: | | ribonuclease<br>desoxyribonuclease |
| Serum proteins: | | albumin<br>immunoglobulins |
| Other proteins: | | lactoferrin<br>C.E.A. |

The protein component of pancreatic juice, also called the ecbolic response, consists of enzymes, immunoglobulins and other proteins such as lactoferrin. The total amount of proteins secreted varies between 10 and 40 grams, which is about one quarter to half of the daily protein intake of an adult. This high rate of turnover of proteins makes the organ susceptible to protein deficiency (Zuidema, 1959; Herman-Taylor, 1972; Gyr, Wolf et al 1975). About 80% of the proteins secreted by the pancreas are enzymes, synthesised by the acinar cells (Jamieson & Palade, 1967[a,b]). See table I.1 for an enumeration of the various proteins and electrolytes.

Of the enzymes, trypsin, formed by the activation of trypsinogen by enterokinase which is present in the brush border of the duodenal mucosa, has the important characteristic that it is able to activate trypsinogen and other inactive precursors of proteolytic and lipolytic enzymes (Desnuelle & Figarella, 1979). The interrelations of the secretion of the various pancreatic enzymes are not constant and their changes little understood (Wormsley & Goldberg, 1972).

Both physiological and clinical studies have drawn attention to the fact that endocrine and exocrine pancreas are intimately related in their function, which is expressed in the composition of pancreatic juice (Henderson, Daniel & Fraser, 1981; Editorial BMJ, 1981).

The composition of pancreatic juice has been found to differ significantly between men and women. After stimulation with exogenous hormones the concentrations of bicarbonate and enzymes was found to be significantly less in women than in men, all healthy subjects (Andriulli, Tapero et al, 1982).

### I.1.2.2. Regulation of exocrine pancreatic secretion.

#### I.1.2.2.1 Stimulation.

Pancreatic secretion is regulated by both neural and hormonal mechanisms which are nowadays considered to be integrated in one system (Harper, 1972; Wormsley, 1977; Harper & Scratcherd, 1979; DiMagno & Go, 1982). Physiological stimulation of pancreatic secretion has been described to occur in three phases.

The 'cephalic phase' is initiated by sensory and psychic stimuli and is effectuated by vagal impulses. Vagal stimulation leads to an increase in protein concentration of the pancreatic juice (Sarles, Dani et al, 1968; Henriksen & Worning, 1974; Singh & Webster, 1978).

The 'gastric phase' is started by food distending the antrum of the stomach. Either gastrin or neural impulses mediate a stimulating influence on protein secretion (Harper & Scratcherd, 1979).

The 'intestinal phase' is by far the most important phase of phsiological stimulation of pancreatic secretion. It begins when food, reaching the duodenum, releases from the mucosal cells two hormones with a profound effect on the exocrine pancreas: secretin and cholecystokinin or pancreozymin.

Secretin is a polypeptide that appears in the circulation when the intraluminal pH of the duodenum becomes less than 4.5 (Schaffalitzky de Muckadell, Fahrenkrug & Rune, 1979). This hormone stimulates the secretion of water and electrolytes by the ductular epithelium of the pancreas (Fölsch & Creutzfeldt, 1977). Secretin probably also increases pancreatic blood flow (Inoue, Kawano et al, 1981). Although the absolute proof that secretin plays a physiological role in the regulation of pancreatic secretion has not been produced, the outlined mechanism has been generally accepted as a working hypothesis (Harper & Scratcherd, 1979; Wormsley, 1980).

Cholecystokinin-pancreozymin (CCK-PZ) is released from the duodenal mucosal cells when food degradation products such as peptide chains and micellar fatty acids come into contact with these cells. Increased levels of circulating CCK-PZ are correlated with a rise in protein concentration of the pancreatic juice (Harper & Scratcherd, 1979).

Analysis of the effects of secretin and CCK-PZ on exocrine pancreatic secretion has been hampered by the fact that until recently all available preparations were contaminated (Sewell & Young, 1975; Arvanitakis, 1976). The introduction of synthetic hormones has helped to elucidate the question of potentiating effects of each hormone on the other. It is now well established that CCK-PZ has a potentiating effect on the secretin stimulated hydraletic reponse but that secretin has no potentiating effect on the CCK-PZ stimulated ecbolic response (Wormsley, 1969[a], Harper, 1972; Henriksen & Worning, 1974; You, Rominger & Chey, 1983).

In the past, it was that secretin stimulates the secretion of enzymes. Except for the fact that the hormone preparations might have been contaminated by CCK-PZ, it is also known now that a so called 'wash out' phenomenon exists. This phenomenon exists of a wash out of proteins already present in the ductular system of the gland at the time that the flow rate is increased by secretin administration. This effect may last for up to 60 minutes in man (Harper & Scratcherd, 1979).

Besides secretin and CCK-PZ, exocrine pancreatic secretion is known to be stimulated by many other substances. Hormones, like caerulein, which is derived from amphibian skin and has CCK-PZ like effects, gastrin, which also stimulates the ecbolic response, and vasoactive intestinal peptide, which stimulates the hydraletic response, may play a role in the physiological regulation of pancreatic secretion (Chey & You, 1980; Holst, Knuhtsen et al, 1983). Corticosteroids also appear to have a stimulatory effect on pancreatic secretion. Chronic

corticosteroid administration in rats increases pancreatic weight and protein output (Bourry & Sarles, 1978). In man, adrenocortical insufficiency was found to be accompanied by a reduction in stimulated pancreatic secretion, which recovered after substitution therapy with steroids (Gullo, Priori and Labo, 1982). Prostaglandin $PGE_1$, adminstered intravenously to dogs, stimulated protein secretion but less strongly than CCK-PZ (Rudick, Gonda et al, 1971). The presence of bile in the duodenum has been found to have a stimulating effect on the hydraletic response to exogenous secretin (Otte, Stahlheber et al,1973[a,b]; Otte, Thurmayr et al, 1976; Osnes, Petersen & Schrumpf, 1978; Osnes, Hansen et al, 1980[a]; Osnes, 1981[a,b]).

The effects of vagal stimulation and of gastrin on pancreatic secretion have been mentioned. It is thus not surprising that several investigators have explored the effects of **GASTRIC SURGERY** on exocrine pancreatic secretion. Truncal vagotomy was found to be followed by reduction in bicarbonate output after stimulation with secretin in one study (Wormsley, 1972[a]), but other authors have not confirmed this finding (Dreiling, Druckerman & Hollander, 1952; Konturek, Popiela & Thor, 1971). Enzyme secretion after truncal vagotomy showed a decreased sensitivity to exogenous hormones but no reduction of secretory capacity (Malagelada, Go & Summerskill, 1974). Parietal cell vagotomy did not impair the hydraletic response to secretin (Berstad, Roland et al, 1976) nor the food stimulated pancreatic secretion (Ramus, Williamson et al, 1982). After partial gastrectomy with a reconstruction that bypasses food from the duodenum, secretin release after a testmeal was reduced (Nishiwaki, Satake et al, 1982). A careful study of exocrine pancreatic secretion after various types of gastric surgery demonstrated that reduced trypsin concentration of duodenal contents was due to rapid gastric emptying and that there was no evidence that this type of surgery is followed by pancreatic insufficiency or even a reduced pancreatic response to exogenous hormones (McGregor, Parent & Meyer, 1977).

I.1.2.2.2 Inhibition.

The inhibition of exocrine pancreatic secretion has been investigated considerably less extensive than the stimulation.

Neural influences with an inhibiting effect comprise of parasympathetic fibers, which have been postulated (Sarles & Sahel, 1976) but not demonstrated (Singer, 1980; Rozé, Chariot & Vaille, 1982), and of sympathetic fibers for which the case is much stronger (Hayama, Magee & White, 1963; Harper, 1972; Kelly, Rose and Nahrwold, 1976, 1977; Rozé, Chariot & Vaille, 1982).

Inhibitory influences have also been reported of several hormones: glucagon (Singh & Webster, 1978); pancreatic polypeptide (Adrian & Bloom, 1976; Chey & You, 1980; Diemel &

Table I.2 Stimulation and inhibition of exocrine pancreatic secretion.

STIMULATING FACTORS.

Hormonal.
Secretin
Cholecystokinin-pancreozymin (CCK-PZ)
Gastrin
Caerulein
Vasoactive intestinal peptide (VIP)
Corticosteroids
Prostaglandin $PGE_1$

Neural.
Parasympathetic

Other:
Intraduodenal bile

INHIBITING FACTORS.

Hormonal.
Glucagon
Pancreas polypeptide (HPP)
Somatostatin
Bombesin

Neural.
Parasympathetic
Sympathetic

Other:
Parenteral nutrition
Elementary diet
Intraduodenal trypsin
High fiber content of diet
Cigarette smoking

Lamers, 1980); somatostatin (Miller, 1980) and bombesin (Chey & You, 1980).

Furthermore, long term parenteral nutrition, especially with hypertonic glucose (Johnson, Schanbacher et al ,1977; Klein, Shnebaum et al, 1983; Variyam, 1983), elementary diet (Keith, 1980), a high fiber content of the diet (Sommer & Kasper, 1980) and cigarette smoking (Bynum, Solomon et al, 1972) have been found to inhibit pancreatic secretion. Table I.2 presents a schematic overview of stimulating nad inhibiting factors.

A negative feedback mechanism of pancreatic secretion has been made likely by the demonstration of an inhibitory effect of intraduodenal trypsin administration whereas withdrawal of pancreatic juice from the duodenum stimulates secretion (Henriksen & Worning, 1974; Ihse & Lilja, 1979; Toskes, 1980; Isaksson & Ihse, 1983).

In summary, the normal exocrine pancreas secretes a watery juice rich in bicarbonate, electrolytes,digestive enzymes and other proteins.The secretion of water and bicarbonate, which serves to neutralise the acid gastric contents in the duodenum in order to create an optimal environment for enzymatic activity, is stimulated by the intestinal hormone secretin. This hormone is released from the duodenal mucosa when the intraluminal pH is lowered. Bicarbonate and electrolytes are secreted by the epithelium of the small ductuli of the pancreas. The enzymes are synthesised and secreted by the acinar cells under the influence of another intestinal hormone, cholecystokinin-pancreozymin, that is released from the duodenal mucosa on contact with food degradation products. The regulation of pancreatic secretion is a complex neurohormonal mechanism in which stimulatory parasympathetic and inhibitory sympathetic impulses participate together with the hormonal factors.
Figure I.4 presents a scematic view of these influences.

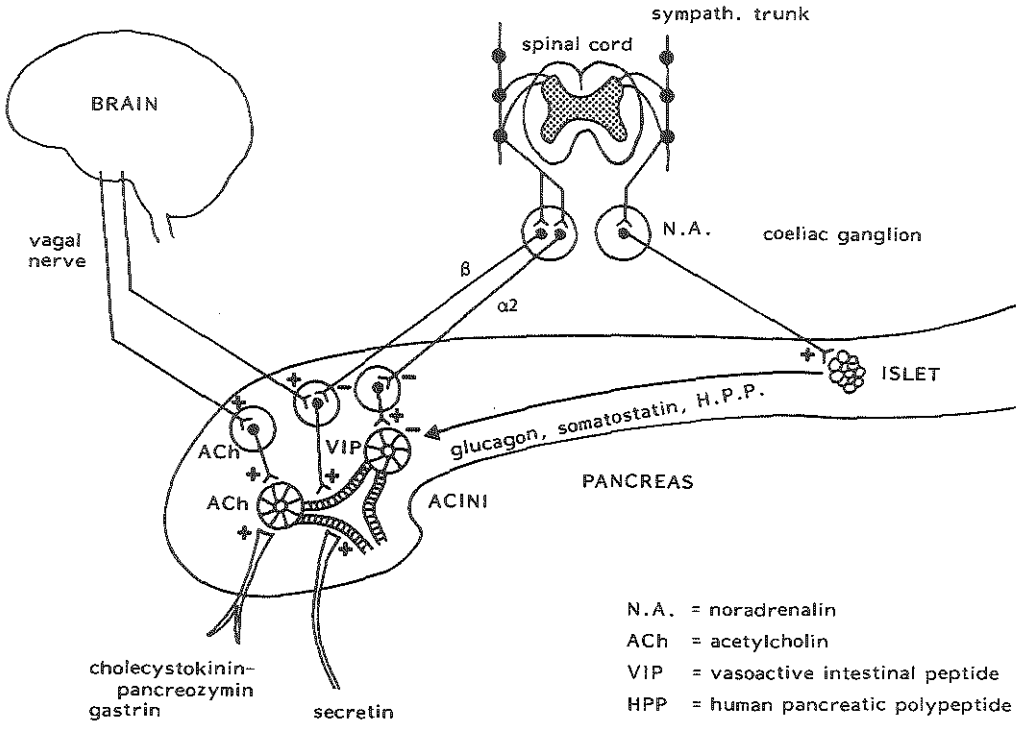



Figure I.4 Schematic representation of stimulatory and inhibitory influences on the exocrine pancreas.

## I.2 THE DISEASED PANCREAS

### I.2.1 Pancreatitis, definitions.

Inaccurate use of the terms acute and chronic pancreatitis may cause great confusion. Therefore in this study we will adhere to the classification of pancreatitis proposed and accepted by the Marseilles' symposium (Sarles, 1965).

Acute pancreatitis is characterised by a complete functional and structural recovery once the acute phase is over, provided the patient survives.

Chronic pancreatitis is defined by the progressive deterioration of function and structure which ultimately leads to the destruction of the gland.

#### I.2.1.1 Acute pancreatitis.

Acute pancreatitis may occur either as a single attack or as a relapsing disease. In Western Europe biliary tract pathology is the main etiological factor. Elimination of the underlying cause will prevent relapses (Dürr, 1979). As the functional integrity of the gland is preserved after recovery of acute pancreatitis, this disease is not relevant for a study on exocrine pancreatic function analysis as diagnostic tool.

#### I.2.1.2 Chronic pancreatitis.

##### I.2.1.2.1 Pathogenesis.

Chronic pancreatitis has been reported from many countries all over the world and has been associated with various etiological factors. Long term abuse of alcohol, possibly in combination with a diet rich in proteins and fat, has received much attention as cause of chronic pancreatitis (Sarles, 1973; Ishii, Nakamura et al, 1973; Durbec, Sarles et al, 1978).

Hyperparathyroidism has been reported to lead to chronic pancreatitis with histological changes similar to those seen in chronic alcoholic pancreatitis (Sarles, Sahel et al, 1979).

Hereditary pancreatitis has been known to occur at an early age (Kattwinckel, Lapey et al, 1973; Williams, Caldwell & Wilson, 1982).

From several tropical countries reports have been published on pancreatic calcifications associated with diabetes in young patients. Alcohol abuse is unusual in these patients and the condition appears to be rather painless (Zuidema, 1959; Shaper, 1964; Banwell & Campbell, 1967; Olurin & Olurin, 1969; Nwokolo & Oli, 1980). Malnutrition has been mentioned as an etiological factor in this 'diabetes of the poor' (Zuidema, 1959), but others have suggested thatchronic cyanide poisoning from cassava might play a role (Pitchumoni & Thomas, 1973).

Several drugs have been incriminated as etiological agents in pancreatitis. Although it is difficult to estimate their exact relevance from the occasional reports available, it is not impossible that some of the so called idiopathic cases of chronic pancreatitis are in fact caused by drugs. Some of the drugs that have been associated with chronic pancreatitis are: steroids (Fleischer, 1978; Mallory & Kern, 1980; Steinberg & Lewis, 1981; Weaver, Bordley et al, 1982); valproic acid (Sasaki, Tonoda et al, 1980) and azathioprin (Sturdevant, Singleton et al, 1979).

Obstruction of the outflow of the pancreatic duct, which may occur in pancreatic tumors, can also lead to chronic inflammatory changes of the gland. The histological changes in these cases are quite different from those seen in the types of chronic pancreatitis mentioned above. Therefore it appears justified to separate the former group of etiologies, leading to a similar histological picture, from pancreatic duct obstruction as a cause of chronic pancreatitis (Payan, Sarles et al, 1972; Sarles &Sahel, 1976; Sarles, Sahel et al, 1979).

Consecutively, the former group will be referred to as chronic parenchymatous or calcifying pancreatitis, while the latter will be named chronic obstructive pancreatitis.

From this distinction it is clear that obstruction plays no etiological role in the development of chronic parenchymatous or calcifying pancreatitis (CPP/CCP). This concept opposes the traditional 'big duct hypothesis' -which considered obstruction of the main duct as the cause of chronic pancreatitis- on the following grounds:

- the histological differences, mentioned already and to be discussed in detail below;
- dilatation of the main duct is by no means the rule in chronic pancreatitis (Grodzinsky, Schuman & Block, 1977);
- alcohol does not cause a lasting stimulation of the pancreatic secretion and can therefore not lead to a significant rise in intraductal pressure as was believed in the past (Singer, 1980).

The pathogenesis of CPP/CCP has been investigated in animals and man by studying the effects of acute and chronic alcohol administration because alcohol appears to be the most important causal factor from epidemiological point of view. Alcohol has been shown to have a toxic effect on the acinar cells of the pancreas by interfering with the cellular energy metabolism through inhibition of oxidation of fatty acids (Estival, Clemente & Ribet, 1980). Accumulation of fat droplets in acinar cells of experimental animals after relatively short periods of alcohol consumption have been seen on electronic microscopy (Noronha, Ferreira de Almeida et al, 1981; Noronha, Bordalo & Dreiling, 1981). Analysis of pancreatic juice in experimental animals and man has demonstrated a rise in protein concentration under the influence of alcohol, which has been attributed to an increased cholinergic tone of the intrapancreatic ganglia (Sarles, Sahel et al, 1980). Also, the bicarbonate concentration of the pancreatic juice of alcoholic subjects has been found to be reduced, possibly due to acetaldehyde, one of the metabolic products of alcohol (Sarles, Sahel et al, 1980). Analysis of the calculi that occur in CPP/CCP has revealed the presence of a protein, that has subsequently been shown to be synthesised by the acinar cells. This protein is able to inhibit the formation of calcium carbonate crystals and it was shown that its concentration in the pancreatic juice of patients with CPP/CCP was lower than in that of controls (DeCaro, Lohse & Sarles, 1979; Lohse, Kraemer & Kaess, 1982; Multigner, DeCaro et al, 1982). It has been suggested that a (relative) deficiency of this 'stone protein' or'pancreolithin' may lead to the calcification of protein precipitates that are formed in the small ductuli of patients who have an increased protein concentration of the pancreatic juice. (Sarles, DeCaro et al, 1983).

In summary, the hypothesis constructed by Sarles and coworkers concerning the pathogenesis of chronic calcifying pancreatitis, that has not been fundamentally combatted by others, consists of the following steps: chronic alcohol consumption increases the cholinergic tone of the intrapancreatic ganglia, thereby increasing the protein: bicarbonate ratio of pancreatic juice; proteins therefore precipitate in the small ductuli and form plugs that obstruct the outflow; a reduced concentration of a substance that inhibits formation of calcium carbonate crystals leads to calcification of the plugs; gradually more and more lobuli become obstructed by formation of plugs and calculi, leading to dilatation of the ductuli and destruction of the acini (Sarles, DeCaro et al, 1983).

The pathogenesis of chronic obstructive pancreatitis is determined by the presence of an obstructing lesion, e.g. a tumor or stenosis of the duct or the papilla.

I.2.1.2.2 Histopathology of chronic pancreatitis.

Chronic pancreatitis in any form is characterised by atrophy of the acinar tissue with fibrous tissue replacement, dilatation of the ductular system with changes of the epithelial lining and by inflammatory reaction (Sarles, Sahel et al, 1979).

Chronic parenchymatous or calcifying pancreatitids has several specific features which distinguish this entity from the obstructive type of chronic pancreatitis (Nakamura, Sarles & Payan, 1972; Payan, Sarles et al, 1972; Sarles & Sahel, 1976):

- a lobular distribution of the lesions which means that the severity of the lesion varies from one lobule to the other: in the early stage of the disease only occasional changes may be seen whereas in the final stages several intact lobules may be found surrounded by fibrous tissue. In obstructive chronic pancreatitis on the other hand, the lesions are evenly distributed over all lobules;
- the appearance of small cysts in the atrophied areas, lined with cubic epithelium and apparently not in communication with the ductular system. Some investigators think that these microscopic cysts represent reduplications of the ductular epithelium (Noronha, Bordalo & Dreiling, 1981). An alternative explanation has been offered by Bockman and coworkers, who have found evidence that the microscopical arrangement of the normal acini is tubular and not like a bunch of grapes. Therefore, the described cysts are considered to be the consequence of acinar dedifferentiation (Bockman, Boydston & Parsa, 1983);
- the ductuli are dilated and contain plugs of protein which may be calcified and which damage the epithelium;
- calcifications are almost always intraductular; they are considered to be a late sign in CPP/CCP (Sarles, Sahel et al, 1979; Bernades, Belghiti et al, 1983); some authors have suggested that there are in fact two types of chronic parenchymatous, pancreatitis, a calcifying type and a non-calcifying type (Rumpf & Pichlmayr, 1982).
- an increase in the number of nerve cells, that may show degenerative changes;
- arteriosclerotic changes of intra- and extrapancreatic vessels;
- the islets in chronic pancreatitis remain intact until the very advanced stages;

The early cellular changes of the acini consist of loss of zymogen granulae and of accumulation of fat droplets (Darle, Ekholm & Edlund, 1970; Tasso, Clop & Sarles, 1971; Noronha, Bordalo & Dreiling, 1981; Noronha, Ferreira de Almeida et al, 1981).

The dilatation of the main pancreatic duct is thought to be caused by fibrous scarring of the periductal tissue. This

mechanism explains the irregular caliber of the main pancreatic duct -the chain of lakes- whereas one would expect a diffuse dilatation in the case of a rise in intraductal pressure (Stolte, 1979).

It has been mentioned before that the histological changes in chronic obstructive pancreatitis are different from those listed above. The typical lobular distribution is absent and dilatation of the main duct is much more conspicuous than dilatation of the small ductuli while protein plugs are scarce or absent. Calcifications are absent in chronic obstructive pancreatitis (Sarles, Sahel et al, 1979) but they may occur in the obstructing lesion itself (Nix, 1981).

At this place mention should be made of the fact that in the process of ageing, atrophy of the acinar tissue of the pancreas with an increase in lipomatous tissue has been reported without clinical symptoms (Walters, 1966). However, occasional reports have drawn attention to a clinical syndrome of painless pancreatic insufficiency in the absence of any of the known etiological factors, particularly alcohol. In these cases extensive acinar atrophy and lipomatous tissue replacement were found at autopsy (Robson & Scott, 1953, Bartholomew, Baggenstoss et al, 1959; FitzGerald, 1972; Stolte, 1979). As all reported patients were elderly it is uncertain whether this syndrome is a separate entity or an exaggeration of the natural ageing process.

### I.2.1.2.3 Pathophysiology

In this section attention will be given to the exocrine functional changes that occur in chronic pancreatitis. Loss of acinar and ductular cells by the destructive processes outlined leads to a diminished secretory capacity of the exocrine pancreas. The exact relationship between morphological or structural and functional changes in chronic pancreatitis is unknown but some well established facts should be mentioned here.

During the passage of pancreatic juice through the ductal system, its composition may change depending on factors like flow rate, diameter of the lumen and integrity of the epithelium. Delayed passage along damaged epithelium may result in a resorption of bicarbonate with a rise in chloride concentration of the pancreatic juice (Dreiling, 1975[a]). Prior to this reduction in bicarbonate concentration in chronic pancreatitis, a phase of electrolyte hypersecretion has been reported (Dreiling & Wolfson, 1979; Neves, Borges & Vilela, 1983), attributed to reduplication of the epithelium of the small ductuli (Dreiling & Wolfson, 1979). Progressive loss of secretory function leads to a response that has a relatively normal volume but reduced concentrations of bicarbonate and enzymes, called qualitative

insufficiency. In the final stages of chronic pancreatitis reduction of volume occurs as well, leading to total insufficiency (Dreiling & Messer, 1978).

Diabetes develops in many patients with chronic pancreatitis in the final stage of the disease (Bernades, Belghiti et al, 1983). Impairment of the exocrine function of the pancreas has, interestingly, been demonstrated in patients with diabetes but without chronic pancreatitis (Chey, Shay & Shuman, 1963; Baron & Navarro, 1973; Frier, Saunders et al, 1976). Insulin is said to potentiate the stimulating effect of CCK-PZ on protein synthesis and deprivation of insulin leads to a reduction of amylase secretion (Henderson, Daniel & Fraser, 1981). On the other hand, when malabsorption exists due to exocrine insufficiency, insulin secretion is decreased because of a reduced demand. Substitution of pancreatic enzymes improves glucose tolerance in these cases (Ebert & Creutzfeldt, 1980; Editorial BMJ, 1981).

### I.2.1.2.4 Clinical aspects and treatment

In this section the clinical aspects of chronic pancreatitis will be discussed. The distinction between chronic parenchymatous and obstructive pancreatitis will be difficult to maintain here, first because the clinical picture of obstructive pancreatitis is usually dominated by the obstructing tumor and second because the clinical signs and symptoms are reportedly similar to those of parenchymatous pancreatitis (Sarles, Sahel et al, 1979).

The most important **SYMPTOM** of chronic pancreatitis nowadays in Western Europe is pain. It has been pointed out that pain was scarcely mentioned in many of the older publications on chronic pancreatitis (FitzGerald, 1972), and pain is also often absent in the tropical forms of chronic pancreatitis (Zuidema, 1959). The mechanism of pain in chronic pancreatitis is not known. Although it has been shown that a rise of intraductal pressure is associated with pain (Madsen & Winkler, 1982), and that many patients become painless in the course of the disease when pancreatic production virtually 'dries up' and intraductal pressures therefore remain low (Ammann, Langiader & Akovbiantz, 1979), others have reported a lack of correlation between pain and dilatation of the main duct (Grodzinsky, Schuman & Block, 1977). One of the reported treatments for chronic pancreatitis was ligation of the pancreatic duct, with good results (Adson, 1979)!

Loss of body weight occurs in the course of the disease due to anorexia and to malnutrition and malabsorption when exocrine insufficiency develops.

During the painful relapses of the disease, fever and jaundice may be present, the latter usually due to compression of the distal common bile duct by oedema of the pancreas. Persisting jaundice is rather infrequent in chronic pancreatitis but may be caused by sclerosis around the intrapancreatic part of the common bile duct (Siegel, Sable et al, 1979; Warshaw & Rattner, 1980; Skellenger, Patterson et al, 1983; Newton, Rittenburg & Anderson, 1983).

Steatorrhoea heralds the development of exocrine insufficiency and occurs in the final phase of the disease.It has been shown to develop when the lipase output in response to CCK-PZ stimulation is reduced to 6-10% of normal (DiMagno, Go & Summerskill, 1973). Steatorrhoea is defined as the excretion of more than 5 grammes of fat per day in the stool.

Diabetes is also a late feature of painful chronic pancreatitis but it may be the first sign in painless and tropical forms of the disease (Zuidema, 1959; FitzGerald, 1972).

The **DIAGNOSTIC ASPECTS** of chronic pancreatitis will be discussed extensively in the next chapter. Criteria for the diagnosis should be laid down here in the presentation of the clinical aspects of the disease. Few authors have stated the diagnostic criteria used for the patients they report on. We intend to adhere to the minimal criteria which have been outlined by Creutzfeldt (Creutzfeldt, Fehr & Schmidt, 1970) and which are also advocated by the 'Japanese Society for the Study of the Pancreas' (Wakasugi, Funakoshi & Ibayashi, 1983):

- histological changes demonstrated and/or
- calcifications on the plain X-ray of the abdomen and/or
- impaired exocrine function in the presence of typical clinical features

Recently, pancreatographical changes have also been adopted as criterium for the diagnosis chronic pancreatitis (Seligson, Cho et al, 1982).

During the course of chronic pancreatitis, several **COMPLICATIONS** may occur. The formation of retention pseudocysts in chronic pancreatitis differs from the pseudocysts in acute pancreatitis in that the former have no tendency to resolve spontaneously (Sarles, Salasc et al, 1982; Aranha, Prinz et al, 1983). Fistulae may form, either externally or internally, extending into the thoracic cavity, the retroperitoneal area or into intraperitoneal organs, notably the bowel. Gastrointestinal haemorrhage may occur by erosion of peripancreatic vessels. The haemorrhage may occur in the main pancreatic duct or directly into the bowel lumen (Van Rooyen, van Blankenstein et al, 1983).

**LIFE EXPECTANCY** in chronic pancreatitis is reduced mainly because of these complications. Furthermore, the development of diabetes in alcoholic subjects often leads to hypoglycaemic attacks (Bernades, Belghiti et al, 1983). No correlation has been demonstrated between chronic pancreatitis and pancreatic cancer, except in hereditary pancreatitis (Kattwinckel, Lapey et al, 1973). On the other hand, the incidence of extrapancreatic cancer has been found to be increased in patients with chronic pancreatitis (Ammann, Knoblauch et al, 1980; Moreaux & Thomson, 1983).

The progressive character of chronic pancreatitis has been demonstrated in a longitudinal study using E.R.C.P. (Nagata, Homma et al, 1981).

**TREATMENT** of chronic pancreatitis in UNCOMPLICATED cases is primarily conservative and aims at relieving pain and regulating diabetes and malabsorption. Acute relapses may require hospital admission with adequate analgesics and elementary or parenteral nutrition to reduce pancreatic secretion (Sarles, Sahel et al, 1979).

Surgical intervention is indicated when conservative measures fail to relieve pain adequately or when complications arise (Warshaw, Popp & Schapiro, 1980; Sarles, 1981; Moreaux & Thompson,1983). Four types of operations for chronic pancreatitis have been advocated.

First, operations on the innervation of the pancreas, excision of the coeliac ganglion or transsection of the splanchnic nerves, have been propagated as methods to interrupt the afferent pain fibers. Because the results have been disappointing in most hands, these operations are seldomly performed nowadays (Frey, Child & Fry, 1976; White & Slavotinek, 1979; Mallet-Guy, 1982).

Second, operations on the papilla of Vater (sphincteroplasty) are indicated in the rare cases of benign papillary stenosis associated with chronic pancreatitis (Sarles, Sahel et al, 1979). As has been outlined above, obstruction at this level is seldomly of etiological importance in chronic pancreatitis and the results of this operation in these patients are poor (White & Slavotinek, 1979).

Third, when the main pancreatic duct is dilated, internal drainage with a loop a small bowel according to the Roux-en-Y method, may be achieved. The anastomosis between the main duct and the loop of bowel can be constructed either side-to-side after longitudinnal incision of the anterior surface of the gland or end-to-end after resection of the tail. Pain relief after drainage operations has been reported in 75% of the patients (Sarles & Delecourt, 1979; White & Salvotinek, 1979; Prince & Greenlee, 1981; Bradley, 1982). It is difficult to understand how pain relief is obtained in these patients because ligation of the main duct (Adson, 1979) or blockade with

Ethibloc (Gall, Mühe & Gebhardt, 1981), procedures which do not decrease intraductal pressures, have also been reported to have beneficial results in chronic pancreatitis. The theoretical advantage of drainage operations is the conservation of pancreatic tissue (Prince & Greenlee, 1981). However, in one follow up study of patients after drainage procedures for chronic pancreatitis a progressive deterioration of both exocrine and endocrine function was demonstrated in spite of patent anastomoses (Warshaw, Popp & Schapiro, 1980). A disadvantage of drainage procedures is the possibility of overlooking a carcinoma in the proximal part of the gland (White & Slavotinek, 1979).

Fourth, resections of the pancreas, either from left to right or partial or total pancreatoduodenectomies have been found to be satisfactory treatment in chronic pancreatitis by many authors (Frey, Child & Fry, 1976; Sato, Noto et al, 1981; Sarles, 1981). Operative mortality increases with the extent of the resection and may amount to 20% after total pancreatectomy (Gebhardt, Gall et al, 1979; Sarles, 1981). Development of diabetes is frequent after major resections and may limit life exspectancy, particularly in alcoholics (Frey, Child and Fry, 1976; Sarles, 1981). The results regarding pain relief are approximately similar for the various types of resctions and amount to 75% good results, provided patients abstain from further alcohol abuse (Frey, Child and Fry, 1976; Eggink, 1981; Sarles, 1981).

Surgical treatment of COMPLICATIONS of chronic pancreatitis must be tailored to the anatomical situation as outlined by preoperative pancreaticography (Sarles, Sahel et al, 1979). It is generally advised to treat not only the complication but also the disease, for instance by drainage or resctions (Sarles, Salasc et al, 1982). As has been mentioned before, pseudocysts in chronic pancreatitis usually have no tendency to resolve spontaneously and thus often require surgical intervention (Sarles, Salasc et al, 1982). Similarly, fistulae often require resectional treatment (Sarles, Sahle et al, 1979). Gastrointestinal haemorrhage as complication of chronic pancreatitis may be life threatening. Recently, visceral angiography to identify the bleeding vessel preoperatively or to enable embolisation to be performed has been shown useful (Stabile, Wilson & Debas, 1983). Common bile duct complications of chronic pancreatitis may lead to biliary cirrhosis if not treated, usually by surgical decompression and/or pancreatic resection (Sarles, Sahel et al, 1979; Warshaw & Rattner, 1980; Gadacz, Lillemoe et al, 1983).

In summary, surgical treatment of chronic pancreatitis is indicated either to obtain pain relief when conservative measures have failed to do so or to deal with complications. The operative mortality may amount to 20% (Sarles, 1981). Pain relief is achieved in about 75% of patients both after drainage and after resections, but long term follow up studies have not been published (Traverso, Thompkins et al, 1979; Sato, Noto et al, 1981). It has been postulated that most, if not all patients with chronic pancreatitis become painless in the end phase of the disease (Ammann, Langiader & Akovbiantz, 1979). The type of operation may be selected on the basis of preoperative pancreaticography. Some surgeons advocate drainage when the main duct is dilated and resection when dilatation is absent (Sarles, 1981). Randomised studies to compare the results of both types of surgery have not been performed. Neither has the suggestion been substantiated that early surgical intervention may halt the progressive course of the disease (Dixon & Englert, 1971; Mallet-Guy, 1982). Therefore, the decision to operate on patients with uncomplicated, painful chronic pancreatitis will have to be made after careful balancing of the risks by surgeon and physician. The importance of abstinence of alcohol abuse must be underlined (Sarles, 1981; Moreaux & Thomsen, 1983).

### I.2.2 Tumors of the pancreas

#### I.2.2.1 Endocrine tumors

The pancreas contains a variety of endocrine cell types or Amine-Precursor Uptake and Decarboxylation (APUD) cells, most of them located in the islets of Langerhans but some are dispersed between the acinar tissue (Pancreatic Polypeptide- or P.P.-producing cells). Neoplasms of these cells are called APUDoma's or named after their specific product, e.g. insulinoma, gastrinoma, glucagonoma. Not infrequently, these tumors are part of a syndrome of multiple endocrine neoplasms (M.E.N.).They occur in combination with hyperparathyroidism and tumors of the hypophysis (M.E.N. I or syndrome of Sipple), and are often only diagnosed during the analysis following the detection of one of the other tumors of the syndrome (Wells, Leight & Ross, 1980). In other cases the tumor is discovered by the effect of its product, e.g. recurrent peptic ulceration in gastrinoma, hypoglycaemia in insulinoma. These endocrine tumors do not behave as space occupying lesions by causing obstruction of the biliary or intestinal tract (Modlin, 1979; Friesen, 1982).

### I.2.2.2 Exocrine tumors

By far the most exocrine tumors of the pancreas are malignant and 75% of these are duct cell carcinoma's, 65% of which are located in the head of the gland (Braganza & Howat, 1979). The increasing frequency with which these tumors are diagnosed has been mentioned before. No specific etiological factors have been identified although relationships with age, sex and geography have been established. The role of alcohol, diet, smoking, biliary tract disease and chronic pancreatitis (except the hereditary type) remains uncertain (McMahon, 1982).

As 85% of the patients appears to have metastases at the time of diagnosis, prognosis is extremely poor. Early diagnosis might improve the results of radical surgery but is hampered by the absence of specific signs or symptoms in the early phase (Morgan & Wormsley, 1977). At the present time, 30% of the exocrine tumors is reported to be resectable and 10% is curable (Moossa, 1982).

Clinical features are pain, weight loss and jaundice, while acute and chronic pancreatitis have been reported to develop distal to an obstructing tumor (Van Waes et al, 1977). Migratory thrombophlebitis and thrombosis may be the first presenting lesion and sometimes the tumor is detected only after metastases elsewhere have been found (Braganza & Howat, 1979; Cassière, McLain et al, 1980).

The pancreas itself may also become the seat of secondary tumors, by ingrowth from neighbouring organs, by spread from peripancreatic lymph gland metastases or (rarely) by haematogenous dissemination (Matthew, 1976; Braganza & Howat, 1979; Fitzgerald & Morrison, 1980).

Diagnostic methods will be discussed in the following chapter. The treatment of pancreatic tumors is primarily surgical: either radical resctions of various extent or palliative bypass operations to relieve obstruction of biliary and gastrointestinal tract (Lord Smith of Marlow, 1979; Herter, Cooperman et al, 1982; Obertop, Bruining et al, 1982). There is little evidence that extensive resections, like regional pancreatectomy, result in better 5-year survival rates than 'limited' operations like the Whipple procedure (J.C.Sarles, personal communication). Similarly, there is no evidence that radiotherapy and chemotherapy improve the survival rates after radical surgery (I.Ihse, personal communication).

Table I.3 Survey of diagnostic procedures in nonacute pancreatic disease.

| | |
|---|---|
| I.3.1 | EXOCRINE PANCREATIC FUNCTION ANALYSIS |
| I.3.1.1 | Analysis of pancreatic secretion |
| I.3.1.1.1 | Analysis of duodenal contents |
| I.3.1.1.1.1 | After endogenous stimulation |
| I.3.1.1.1.2 | After exogenous stimulation |
| I.3.1.1.2 | Analysis of pure pancreatic juice |
| I.3.1.1.3 | Estimation of specific substances |
| I.3.1.2 | Noninvasive tests of exocrine pancreatic function |
| I.3.1.2.1 | Serum estimations |
| I.3.1.2.1.1 | Evocative tests |
| I.3.1.2.1.2 | Hormone levels |
| I.3.1.2.1.3 | Tumor markers |
| I.3.1.2.2 | Faecal estimations |
| I.3.1.2.2.1 | Faecal fat excretion |
| I.3.1.2.2.2 | Faecal chymotrypsin concentration |
| I.3.1.2.3 | Urine estimations |
| I.3.1.2.3.1 | Para Amino Benzoic Acid (P.A.B.A.) test |
| I.3.1.2.3.2 | Pancreolauryl test |
| I.3.2 | CYTOLOGICAL ANALYSIS OF PANCREATIC MATERIAL |
| I.3.3 | IMAGING PROCEDURES |
| I.3.3.1 | Plain abdominal X-ray |
| I.3.3.2 | Hypotonic duodenography |
| I.3.3.3 | Endoscopic retrograde cholangiopancreatography |
| I.3.3.4 | Computer tomography |
| I.3.3.5 | Radioisotope scan |
| I.3.3.6 | Angiography |
| I.3.3.7 | Ultrasound |
| I.3.3.8 | Intravenous cholangiography |
| I.3.3.9 | Laparoscopy |

## I.3 DIAGNOSTIC ASPECTS OF NONACUTE PANCREATIC DISEASE

One of the aims of the study presented in this thesis is to assess the clinical relevance of a diagnostic procedure in nonacute pancreatic disease, exocrine pancreatic function testing. Therefore, in this chapter, a number of diagnostic procedures for pancreatic disease currently available will be reviewed. See also table I.3. Special attention will be paid to the indications and limits of each procedure, to its diagnostic performance and to its ability to differentiate between chronic pancreatitis and pancreatic cancer.

### I.3.1 Analysis of exocrine pancreatic function

Analysis of exocrine pancreatic function is based on the assumption that the maximal secretory response is related to the amount of functioning pancreatic tissue (Scratcherd, 1975). A closer relationship between structural and functional changes in nonacute pancreatic disease has not been outlined (Wormsley, 1978). Some of the causes of impaired exocrine pancreatic function are given in table I.4.

Table I.4 Some causes of exocrine pancreatic insufficiency (Howat & Braganza, 1979; Mitchell, Playforth et al 1983)

Chronic pancreatitis
Primary or secondary tumors
Mucoviscidosis (cystic fibrosis)
Primary atrophy (lipomatosis)
Convalescence after acute pancreatitis
Malnutrition

One or more of the following faculties of the exocrine pancreas may be measured:

- The secretory capacity: by estimating the flow rate of and concentrations of electrolytes and enzymes in pancreatic juice. Assessment of the secretory capacity can be performed either in pure pancreatic juice or in duodenal contents. Pancreatic secretion may be stimulated directly by exogenous hormones or indirectly by a testmeal. In the pancreatic production thus obtained, several parameters may be measured:

= volume or flow rate
= concentration of electrolytes (hydraletic response)
= concentration of enzymes (ecbolic response)
= concentration of other substances like lactoferrin

- The synthetic capacity: by measuring the rate of incorporation of labeled amino acids

and, derived from these:

- The digestive capacity: measured by indirect methods (e.g. faecal fat excretion, P.A.B.A. splitting) which involve extrapancreatic factors as well

I.3.1.1 Analysis of pancreatic juice

I.3.1.1.1 Analysis of duodenal contents

I.3.1.1.1.1 After endogenous stimulation

Analysis of duodenal contents after endogenous stimulation of the exocrine pancreas as a diagnostic procedure was described by Lundh and this procedure has since been named after the author (Lundh, 1962). After ingestion of a standard test meal, duodenal contents are sampled through a duodenal tube and enzyme concentrations are estimated in this material.

The reported advantage of this method are the relatively low cost and the avoidance of the side effects of exogenous hormones (James, 1973). Disadvantages are:
- the inability to recognise secretory patterns, as described by Dreiling (Dreiling & Janowitz, 1962).
- submaximal stimulation of the pancreas, which makes quantification of the secretory cell mass impossible (Scratcherd, 1975; Braganza & Rao, 1978)
- influence of extrapancreatic factors such as integrity of the duodenal mucosa and the rate of gastric emptying on the test result (Dreiling, 1975[b]; Wormsley, 1978).

The reported performance of the Lundh test in the diagnosis of chronic pancreatitis is fairly satisfactory (Cook, 1967; Coene & Ten Thije, 1971; Salmon, 1975; Waller, 1975; Gyr, Stalder et al, 1976; Kugelborg, Ihse et al, 1977) but less favourable results have been published as well (Mottaleb, 1973; Dreiling, 1975[b]; Wormsley, 1978). Patient selection might explain these differences as the results have been generally most accurate in patients with advanced disease of the pancreas.

Table I.5 Hormone preparations used in exocrine pancreatic function testing.

Secretin preparations.

| | Manufacturer | Unit | Relative strength |
|---|---|---|---|
| Natural | Boots' | CHR | 1 CU = 2-8 CHR |
| | GIH | CU | |
| Synthetic | Squibb | mug | 1 mug = 5.4 CU |

Cholecystokinin-pancreozymin preparations.

| | Manufacturer | Unit | Relative strength |
|---|---|---|---|
| Natural | Boots' | CHR | 1 mg = 5 CHR |
| | GIH | IDU | 1 IDU = 4 CHR |
| Synthetic (sincalide) | Squibb | mug | 1 mug = 30 IDU |
| Caerulein | Farmitalia | ng | |

Legend:
CHR = Crick Harper Row units
GIH = Gastrointestinal Hormone, Karolinska Institute, Stockholm
CU = Clinical unit
IDU = Ivy Dog Unit

References: Wormsley, 1969[a,b]
Ondetti, Rubin et al, 1970
Bourke, Swann et al, 1972
Gutierrez & Baron, 1972
Harper, 1972
Thulin, 1973
Dockray, 1973
Arvanitakis, 1978

I.3.1.1.1.2 Analysis of duodenal contents after exogenous stimulation

The basal or interdigestive production of the exocrine pancreas is highly variable and therefore not suitable for use in the diagnosis of pancreatic disease (DiMagno & Go, 1982).

As has been outlined above, stimulation of the exocrine pancreas with exogenous hormones is assumed to allow quantification of the secretory cell mass. Many variations of stimulation schemes and of analytic procedures have been reported, making comparison of the various procedures rather difficult (Göwenlock, 1977).

Sampling of the duodenal contents after exogenous stimulation is usually done with a double lumen tube, which allows separate aspiration of gastric contents to prevent contamination of the duodenal material. Positioning of the tip of the tube near the ligament of Treitz does not usually cause problems in experienced hands unless the anatomy has been grossly altered by previous surgery. Estimations of recovery rates has demonstrated that reliable quantitative sampling of duodenal contents is possible in this way (Lagerlöf, Schütz & Holmer, 1967; Schütz, Anderson & Lagerlöf, 1969; Tympner, 1974[b])

The duodenal contents sampled are a mixture of:
- pancreatic juice
- bile
- duodenal juice
- refluxing intestinal contents

Table I.5 presents a list of preparations available for the exogenous stimulation of the pancreas.

The secretin test was described as early as 1936 and is still used nowadays (Agren & Lagerlöf, 1936). After administration of secretin intravenously, duodenal contents are sampled and analysed for the concentration of bicarbonate and one or more enzymes. Dreiling (Dreiling & Janowitz, 1962; Dreiling, 1975[b]),reportingthe results of 5000 secretin tests, distinguished several secretorypatterns, related to various stages of pancreatic disease:

| | |
|---|---|
| - hypersecretion | an increased flow rate with normal concentrations of electrolytes and enzymes, seen in early chronic pancreatitis; |
| - isolated enzyme deficiency | seen in malnutrition |
| - quantitative insufficiency | a reduced flow rate with normal concentrations of electrolytes and enzymes, seen in pancreatic cancer due to outflow obstruction; |

| | |
|---|---|
| - qualitative insufficiency | reduced concentrations of enzymes and electrolytes with a normal flow rate, seen in chronic pancreatitis; |
| - total insufficiency | reduction of both flow rate and concentrations of electrolytes and enzymes, seen in the final phases of chronic pancreatitis and tumor of the pancreas; |

Dreiling and coworkers have also described the 'augmented secretin test' in which supramaximal doses of secretin are administered in order to quantify secretory cell mass. When applied to patients with an abnormal standard secretin test, the augmented test is said to differentiate between chronic pancreatitis and pancreatic cancer: in the former group a fixed bicarbonate response is seen while the latter group shows a fixed volume response(compared to the results of the standard test) (Dreiling & Messer, 1978; Dreiling & Wolfson, 1979).

Interestingly, Dreiling has advocated expressing the results of the secretin test in values per kg. body weight in order to reduce variance (Dreiling & Janowitz, 1962). Other investigators have not been able to confirm the usefulness of correction for body weight (Burton, Evans et al, 1960; Bourke, Swann et al, 1972).

The secretin-cholecystokinin test was described in 1960, several years after the isolation of cholecystokinin or pancreozymin (CCK-PZ) (Burton, Evans et al,1960). Secretin and CCK-PZ were adminstered sequentially as i.v. boluses. It was found that enzyme estimations in duodenal contents after CCK-PZ did improve the diagnostic performance of the test because in patients with chronic pancreatitis reductions in enzyme concentrations preceded impairment of the hydraletic response. Also, the variance of enzyme concentrations appeared to be much smaller after stimulation with secretin and CCK-Pz than after stimulation with secretin alone. Since that time, the secretin-CCK test, as it is usually called, has been applied in many forms with variations in type of stimulation (simultaneous or sequential administration, bolus or infusion, dosage, type of preparation), in the length of the sampling period, and in the selection of the estimated parameters, see tables I.6 and I.8).

Several comparative studies on the effects of various methods of stimulation have been published. Some have demonstrated no difference between bolus and infusion of the hormones (Tympner, Domschke et al, 1974; Farini, Del Favero et al, 1977), but others found better results with infusion of secretin and CCK-PZ (Wormsley, 1969[a,b]; Gullo, Costa & Labo, 1978). The question whether to give the hormones simultaneously

Table I.6 Comparison of various stimulation schemes

| | |
|---|---|
| Secretin, i.v. bolus: | |
| Boots' 1 CHRU/kg | Adler, Waye & Dreiling, 1976<br>Dreiling & Janowitz, 1962<br>Baron & Navarro, 1973<br>Gutierrez & Baron, 1972<br>Mackie, Cooper et al, 1979 |
| Boots' 1+7½ CHRU/kg | Lagerlöf, Schütz & Holmer, 1976 |
| GIH 1 CU/kg | Osnes, 1978 |
| Secretin + CCK-PZ, i.v. shot, simultaneously or sequentially | |
| Boots' 1-2 U/kg each | Bourke, Swann et al, 1972<br>Burton, Evans et al, 1960<br>Braganza & Rao, 1978<br>Hadorn, Johansen & Anderson, 1968<br>Nakano, Horiguchi et al, 1974 |
| Boots' secretin & GIH CCK-PZ 1 U/kg | Otte, Stahlheber et al, 1973<br>Thurmayr, Thurmayr & Otte, 1975 |
| Boots' secretin & caerulein 30 ng/kg | Gislon, Lefèvre et al, 1976 |
| GIH secretin & CCK-PZ 1 U/kg | Ammann, 1967<br>Dobrilla, Fratton et al, 1976<br>Rolny, 1980 |

Table I.6 cont'd

Secretin + CCK-PZ, i.v. infusion

| | |
|---|---|
| Boots' secretin & CCK-PZ | Pascal, Sannou & Ribet, 1968<br>Ribet, Pascal & Vaysse, 1969 |
| GIH secretin & CCK-PZ | Farini, Del Favero et al, 1977<br>Frier, Saunders et al ,1976<br>Goldberg, Sale et al, 1972<br>Nundy, Shirley et al, 1974<br>Tympner, Domschke et al, 1974[a]<br>Valentini, Cavallini et al, 1981<br>Wormsley, 1969[a,b] |
| Secretin(GIH) + caerulein | Hoeden, Mesa & Delcourt, 1976<br>Tittobello, Testoni et al, 1980 |
| Secretin(GIH) + sincalide | Regan, Go & DiMagno, 1980 |

or sequentially, i.e. secretin or CCK-PZ first, has not been the subject of comparative studies. Dose response relations have been investigated in several reports. Wormsley found a maximal hydraletic response after 10 CHRU Boots' secretin/kg/hr compared to 25 U/kg/hr and to 2 U/kg as bolus (Wormsley, 1968[a]). Others have found lower doses of secretin equally effective: 0.7 U GIH secretin/kg/hr (Petersen & Myren, 1975) and 0.9 U GIH secretin/kg/hr (Konturek, 1970). For CCK-PZ, high doses (4 IDU GIH CCK-PZ/kg/hr) were found to evoke better enzyme responses than 1 IDU/kg/hr, but the higher doses caused more undesirable side effects like abdominal pain and nausea (Wormsley, 1969[a,b]; Goldberg, Sale et al, 1972). A combination of synthetic CCK-octapeptide 40 ng/kg/hr and GIH secretin ½ CU/kg/hr administered simultaneously was found to cause maximal hydraletic and ecbolic responses in healthy volunteers (Regan, Go & DiMagno, 1980).

As for the length of the sampling period, it has been demonstrated that the differences between patients with pancreatic diseases and controls increase after 60 min. of stimulation (Gullo, Costa et al, 1976; Gullo, Costa & Labo, 1978). Therefore it seems advisable to continue sampling for at least 90 minutes.

All studies agree on the importance of measuring the hydraletic response by estimating volume and bicarbonate concentration of the pancreatic juice. Less unanimity exists on the subject of the choice of enzymes to be estimated. Although some authors state that lipase is the most sensitive enzyme for the detection of pancreatic disease (Minaire, Descos et al, 1973; DiMagno, Malagelada & Go, 1975), others have not been able to confirm this statement.

The reported studies differ not only in the methods used but also in their aims. The earlier studies mainly tried to assess the diagnostic performance of the secretin-CCK test in various groups of patients. Later series aimed to compare several methods of stimulation with each other and/or with other diagnostic procedures. In some studies an attempt has been made to clarify the pathophysiology of chronic pancreatitis through exocrine function testing (Dreiling & Messer, 1978; Dreiling & Wolfson, 1979).

When comparing these studies, it should be stressed that selection of patients and controls varies greatly. Some authors have taken healthy volunteers as controls in order to calculate reference values (Burton, Evans et al, 1960; Lagerlöf, Schütz & Holmer, 1967; Gislon, Lefèvre et al, 1976; Farini, Del Favero et al, 1977). The resulting situation is not really comparable to the clinical circumstances where the secretin-CCK test is required to differentiate between patients with pancreatic disease and patients with similar signs and symptoms but without pancreatic pathology. Also, the selection of patients with pancreatic disease shows wide varation in the reviewed papers.

It is easily understood that the diagnostic accuracy of a test will increase with severity of the investigated lesions. Table I.7 presents the relative proportions of patients with advanced chronic pancreatitis, as judged by the presence of calcifications, diabetes or the fact that pancreatic surgery had to be performed, in a number of studies. Similar arguments hold true for patients with pancreatic cancer. In the studies of Bourke, all patients were jaundiced, which might be taken as an indicator of advanced pancreatic cancer (Bourke, Swann et al, 1972). Most other authors do not mention the stage nor the localisation of the tumors in their patients.

Table I.7 Relative proportions of patients with advanced chronic pancreatitis in several studies

| Author & Year | Number of patients | Percentage with Calcifications | Diabetes | Surgery |
|---|---|---|---|---|
| Ammann, 1967 | 22 | 36 | nr | 18 |
| Braganza, 1978 | 17 | 47 | 24 | 12 |
| Capitaine, 1980 | 14 | 100 | nr | 100 |
| Gislon, 1976 | 25 | 76 | 64 | nr |
| Gullo, 1976 | 29 | 62 | nr | 31 |
| Otte, 1973 | 220 | 31 | nr | 37 |

nr = not reported

The method of interpretation of the test data, i.e. the way in which it was decided that the test result was normal or abnormal, also shows great differences between the various series.

Most authors have calculated reference values in either healthy volunteers or in control patients, and applied these values to the group of patients suspected to have pancreatic disease (Dreiling & Janowitz, 1962; Cooper, Moossa et al, 1978; Rolny, 1980). The transfer of values form one group of subjects to another has been shown to be a procedure that easily leads to wrong conclusions (Bezemer, 1981). Another difficulty that presents itself when this method is used, is the selection of parameters: particularly in early and moderately advanced cases some but not all parameters measured may be abnormal. This calls for a specific solution, that is not offered by most authors (Burton, Evans et al, 1960; Lagerlöf, Schütz & Holmer, 1967; Ammann, 1967; Otte, Stahlheber et al, 1973).

Several authors judge the test data by distinguishing various types of secretory patterns, e.g. quantitative insufficiency, total insufficiency (Dreiling & Janowitz, 1962; Bourke, Swann et al, 1972; Adler, Waye & Dreiling, 1976). This method does not eliminate the need for reference values, but it circum-

Table I.8 Diagnostic performance of secretin-CCK tests in the literature.

| Author | Sensitivity | Specificity | Predictability Positive | Predictability Negative | Accuracy |
|---|---|---|---|---|---|
| Adler,1976 | 83(CP) | 88 | 91 | 78 | 85 |
| | 100(ca) | | | | |
| Ammann,1967 | 91(CP) | 100 | 100 | 94 | 92 |
| | 63(ca) | | | 92 | |
| Bourke,1978 | 76(ca) | 93 | 90 | 83 | 85 |
| Braganza,'78 | 88(CP) | 100 | 100 | 92 | 95 |
| Capitaine,'71 | 97(CP) | 100 | 100 | 98 | 99 |
| DiMagno,'77 | 88 | 80 | 80 | 85 | |
| Dreiling,'62 | 99(CP) | 95 | 76 | 100 | 96 |
| | 78(ca) | 95 | 73 | 96 | 92 |
| Farini,'77 | | | | | 94(CP) |
| | | | | | 100(ca) |
| Goldberg,'72 | 80(CP) | 100 | 100 | 98 | 98 |
| | 75(ca) | 100 | 100 | 98 | 96 |
| Hoeden,'76 | 100(CP) | 84 | 85 | 100 | 92 |
| Lagerlöf,'67 | 75(CP) | 100 | 100 | 83 | 89 |
| Nakano,'74 | 86(CP) | 74 | 51 | 94 | 77 |
| | 100(ca) | 74 | 29 | 100 | 76 |
| Nundy,'74 | | | | | 70 |
| Otte,'73 | 97 | 93 | 97 | 93 | 96 |
| Mackie,'79 | 70 | 72 | 76 | 65 | 70 |
| Ribet,'69 | 75(CP) | 100 | 100 | 96 | 97 |
| Rolny,'80 | 96(CP) | 88 | 87 | 96 | 92 |
| | 80(ca) | | 60 | 95 | 86 |
| Thurmayr,'75 | 75(CP) | 98 | 91 | 93 | 92 |
| Tittobello'80 | 79(CP) | 67 | 85 | 57 | 75 |
| Tympner,'78 | 100(CP) | 62 | 79 | 100 | 84 |
| Valentini'81 | 78(CP) | 59 | 68 | 71 | 69 |
| Wormsley,'69 | 100 | 100 | 100 | 100 | 100 |
| Zieve,'66 | 79(CP) | 78 | 83 | 73 | 79 |
| | 100(ca) | 78 | 84 | 73 | 90 |

vents the difficulty of interpreting several parameters at the same time.

The most appropriate method to interprete multiple data of several groups of subjects is discriminant analysis. This procedure has been applied only sporadically to the data of exocrine pancreatic function tests (Capitaine, Cros et al, 1971; Thurmayr, Thurmayr & Otte, 1975).

In summary, in spite of the listed differences in methods and type of patients, it appears useful to compare the diagnostic performance of the secretin-CCK test in various series. Table I.8 lists a number of studies with the diagnostic indices obtained.

Sensitivity is the percentage of abnormal ('positive') tests in patients with the disease that is looked for. Specificity is the percentage of normal ('negative') tests in people without the disease. Positive predictability is the proportion of the patients with an abnormal test that has the disease. Negative predictability is the proportion of patients with a normal test that do not have the disease. The accuracy rate represents the total percentage of correct (positive and negative) tests. In those studies were these figures were not recorded, they have been calculated when possible.

It may be concluded from these data that there are wide variations in diagnostic performance. These variations appear to be more often due to patient selection than to the methodology of the test. Thus, no method appears to be superior. In general, sensitivity and specificty are rather similar in most reports, as are positive and negative predictability. Both papers in which discriminant analysis was applied, show a relatively high diagnostic performance.

### I.3.1.1.2 Analysis of pure pancreatic juice.

Analysis of pure pancreatic juice obtained by endoscopic cannulation of the papilla appears to have several theoretical advantages over the analysis of duodenal contents:

- Pancreatic enzymes are not activated by duodenal enterokinase
- Quantitative sampling
- Possibility to combine sampling with pancreatography in one session.

In clinical practice, however, these advantages have not been substantiated. In one study, no differences were found between the results of pure pancreatic juice analysis and the results of the secretin-CCK test for the diagnosis of chronic pancreatitis (Cremer, Robberecht et al, 1976). In another study, people with a normal pancreatography appeared to have lower enzyme concentrations in pure pancreatic juice than in duodenal contents (Osnes, Petersen & Schrumpf, 1978). Another

disadvantage of pure juice sampling is the high failure rate: Goodale and coworkers were unable to obtain a sufficient quantity of pure pancreatic juice in half of the patients with chronic pancreatitis and pancreatic cancer (Goodale, Condie et al, 1979; 1981). In those cases were cannulation and sampling were succesful, higher levels of albumin, IgA and IgG were found in patients with pancreatic cancer compared to patients with chronic pancreatitis and controls (Goodale, Condie et al, 1979)

I.3.1.1.3 Estimation of specific substances in duodenal contents and pancreatic juice.

Radioisotopes.

The intravenous administration of $^{75}$Se-selenomethionine will be followed by concentration of this isotope in the pancreas with subsequential excretion of the isotope in pancreatic juice. The rate of excretion is considered a parameter of exocrine pancreatic function (Testa, 1979). Nevertheless, in one study no statistically significant differences in excretion rates were demonstrated between patients with exocrine insufficiency and controls (Pointner & Kletter, 1980). In another study, patients with chronic pancreatitis were even found to have higher protein synthesis rates than controls (Boyd, Wood et al, 1982). The use of $^{11}$C-L-methionine instead of $^{75}$Se-selenomethionine did not yield a better diagnostic performance than the secretin-CCK test (Syrota, Dop-Ngassa et al, 1981).

DiMethylOxazolidinedione (D.M.O.) .

Noda and coworkers performed several studies on the excretion in pancreatic juice of D.M.O., a metabolite of the anti-epileptic drug trimethadione. After oral ingestion of this drug, pancreatic excretion of D.M.O. was found to be correlated to the flow rate of pancreatic juice (Noda, Hayakawa et al, 1975[a]). Therefore, this substance was thought to be relevant in the diagnosis of pancreatic disease. In early chronic pancreatitis the authors found signs of a diffusion barrier toD.M.O. with a normal flow rate and a low concentration of D.M.O., while in advanced cases signs of an outflow barrier with a low flow rate could be demonstrated (Noda, Hayakawa et al, 1975[b]). Clinical application of this test showed a diagnostic accuracy of 100% (Noda, Hayakawa et al, 1978). The D.M.O. excretion was found to be superior as diagnostic procedure to the secretin-CCK test (Noda, Hayakawa et al, 1983). No confirmatory reports from other sources have been published in the accessible literature.

Lactoferrin.

Lactoferrin is an iron binding protein with bacteriostatic properties that is present in leucocytes and in several exocrine secretions (De Vet, 1975). Lactoferrin has been demonstrated in acinar cells and pancreatic juice of healthy subjects. In patients with chronic pancreatitis its concentration both in acinar cells and in pancreatic juice appeared to be significantly increased compared to controls (Estevenon, Sarles & Figarella, 1975; Colomb, Pianetta et al, 1976; Multigner, Figarella et al, 1980; Fedail, Harvey et al, 1979; Hayakawa, Harada et al, 1983). Also in duodenal contents, the concentration of lactoferrin was found to be significantly higher in patients with chronic patients than in controls (Multigner, Figarella & Sarles, 1981). On the basis of lactoferrin concentrations in duodenal contents, it was possible to separate patients with pancreatic cancer from patients with chronic pancreatitis (Multigner, Figarella & Sarles, 1981).

Serum proteins.

Pancreatic juice contains not only digestive enzymes but also serum proteins like albumin and immunoglobulins. In patients with chronic pancreatitis and pancreatic cancer increased concentrations of albumin were found in pure pancreatic juice, possibly due to leakage through damaged ductal epithelium (Multigner, Figarella et al, 1980). Conflicting reports have appeared on the concentrations of immunoglobulins in chronic pancreatitis and pancreatic cancer (Bramis, Messer et al, 1978; Dreiling & Wolfson, 1979; Goodale, Condie et al, 1979; 1981). These estimations have no clinical impact at the present moment.

Tumor markers.

Levels of carcino embryonic antigen (CEA) and of pancreatic oncofoetal antigen (POA) have been estimated in pure pancreatic juice and in duodenal contents by several investigators in an attempt to differentiate between pancreatic cancer and chronic pancreatitis, but to no avail (Cooper, Moossa et al, 1978; Capitaine, Voirol et al, 1980; Farini, Nitti et al, 1990; Rolny, 1980). Interestingly, DiMagno and coworkers found higher levels of CEA in the duodenal contents of patients with tumors located distally in the pancreas compared to patients with proximal tumors (DiMagno, Malagelada et al, 1977). In another study, the same group found higher levels of CEA in the duodenal contents of nonicteric patients compared to icteric patients with pancreatic cancer (Go, Taylor & DiMagno, 1981).

### I.3.1.2 Other tests of exocrine pancreatic function

In this section a number of tests will be reviewed that are designed to assess pancreatic exocrine function by noninvasive or indirect methods. The oldest procedure in this respect is the faecal fat excretion test. Recently, other techniques trying to circumvent intubation of the duodenum like serum estimations and analysis of urine for split products, have been introduced.

#### I.3.1.2.1 Serum estimations.

##### I.3.1.2.1.1 Evocative tests of pancreatic enzymes.

It has been known for some time that serum levels of pancreatic enzymes are raised in acute pancreatitis, although it is not clear via which route they reach the circulation (Lake-Bakaar, Rubio et al, 1980; Lake-Bakaar, Smith-Laing & Summerfield, 1982; Toskes, 1982[b]). Based on the assumption that an obstruction to the outflow of the pancreatic duct might cause this phenomenon, attempts have been made to provoke a rise in serum enzyme levels in chronic pancreatitis by stimulation with secretin and CCK-PZ (Burton, Hammond et al, 1960; Schirmeister, Kraut et al, 1975; Howat & Braganza, 1979; Otte, 1979). Also, blockade of the outflow by morphine has been applied (Kim, Schwartz & Sherlock, 1980). The results of these tests were poor, possibly due to the rather insensitive substrate assays that were used to estimate the enzyme concentrations. The development of radioimmunoassay techniques has renewed interest in serum enzyme levels for the diagnosis of nonacute pancreatic disease.

Basal levels of serum trypsin immunoreactivity were found to be decreased in patients with chronic pancreatitis in several studies (Gullo, Ventrucci et al, 1980; Andriulli, Masoero et al, 1981; Masoero, Andriulli et al, 1982).

After stimulation of the pancreas with intravenous secretin patients with mild and moderate chronic pancreatitis exhibited a higher rise in serum trypsin levels than controls (Vezzadini, Gullo & Sternini, 1980). It seems possible therefore, to improve the diagnostic performance of the evocative tests by more sensitive enzyme estimations (Koop, Lankisch et al, 1980).

##### I.3.1.2.1.2 Serum levels of pancreatic polypeptide (HPP).

Human pancreatic polypeptide (HPP) is a substance to which hormonal properties are ascribed. It is produced in the pancreas, both in islet cells and in PP-cells dispersed between the acini (Adrian & Bloom, 1977; Chey & You, 1980). Although its

physiological role has not yet been elucidated, it is known to have an inhibitory effect on exocrine pancreatic secretion (Adrian & Bloom, 1977; Chey & You, 1980). Patients with exocrine pancreatic insufficiency have been shown to have significantly smaller increases of serum HPP levels after meals than controls (Diemel & Lamers, 1980; Andersen, Hagen et al, 1980). Also, a positive correlation between the increase in serum HPP levels after meals and the results of the secretin-CCK test has been demonstrated (Yamamura, Mori et al, 1981; Owyang, Scarpello & Vinik, 1982). No large scale studies on the diagnostic performance of HPP estimations in chronic pancreatitis have been published.

I.3.1.2.1.3 Tumor markers in serum.

Several reports have failed to demonstrate any value of the estmation of tumormarkers like CEA and POA in serum for the diagnosis of pancreatic cancer (Fitzgerald, Fortner et al, 1978; Braganza & Howat, 1979; Mackie, Cooper et al, 1979). It has been suggested but not confirmed that these markers might be useful in the follow up of patients after treatment for pancreatic cancer (Arvanitakis, 1978).

I.3.1.2.2 Faecal estimations.

I.3.1.2.2.1 Faecal fat excretion.

Quantitative assessment of the relative proportion of fat digested is possible when the amounts of fat ingested and excreted are compared. Normally, the fat resorption coëfficiënt should be at least 93%. A lower figure indicates pancreatic insufficiency, clinically apparent as steatorrhoea. This test is evidently not of any use for the diagnosis of early and moderate chronic pancreatitis, because exocrine insufficiency does only occur in the final stages of the disease (Arvanitakis, 1978; Howat & Braganza, 1979).

I.3.1.2.2.2 Faecal chymotrypsin concentration.

A reduction of the amount of chymotrypsin excreted in the faeces has been taken as an indicator of exocrine pancreatic insufficiency (Haverback, Dyce et al, 1963). Significant and clinically applicable differences were found between the faecal chymotrypsin levels of patients with chronic pancreatitis and patients with nonpancreatic malabsorption in this study. There was no evidence that 24 hours sampling yielded results superior to random specimens. In a study using random specimens with radioactive markers, only patients with advanced pancreatic disease were identified (Gilat, Gelman-Malachi & Ronen, 1976).

Similar results were obtained by others (Adham, Dyce et al, 1967; Muller, Wisniewsky & Hansky, 1970; Sale, Goldberg et al, 1974; Dürr, Otte et al, 1978).

I.3.1.2.3 Urine estimations.

I.3.1.2.3.1 Para Amino Benzoic Acid (P.A.B.A:) test

After oral ingestion of the compound substance N-benzoyl-L-tyrosyl-paraaminobezoic acid, chymotrypsin will split off the P.A.B.A. which is subsequently absorbed from the intestine and excreted in the urine. The relative proportion of P.A.B.A. that is recovered in the urine within 8 hours after ingestion is a parameter of exocrine pancreatic function and should be at least 50% (Imondi, Stradley & Wohlgemuth, 1972).

Clinical application of this test in a small group of patients with chronic pancreatitis and pancreatic cancer showed a considerable overlap of values of patients and controls (Arvanitakis, 1976). A larger series of patients yielded a better diagnostic performance: a sensitivity of 76-86% and a specificity of 90-93% for patients with chronic pancreatitis and pancreatic cancer (Lang, Gyr et al, 1981).

An interesting aspect of the P.A.B.A. test was highlighted in a study demonstrating a rise in P.A.B.A. recovery after administration of antacids to patients with chronic pancreatitis (Kimura, Wakasugi & Ibayashi, 1981). The authors suggest that the P.A.B.A. recovery rate is not (only) dependent on the concentration of chymotrypsin in the duodenum but also on the pH as a low pH may inactivate the enzymes. Supportive evidence for this theory was provided by others (Hoek, Sanders et al, 1981).

I.3.1.2.3.2 Pancreolauryl test.

This test has similar properties to the P.A.B.A. test. It is based on the cleavage of a dye, dylaurate-fluorescein, by chymotrypsin, after which the concentration of the dye is estimated in the urine. The diagnostic performance appears to be comparable to that of the P.A.B.A. test (Barry, Barry et al, 1982; Kay, Hine & Braganza, 1982; Lankisch, Schreiber & Otto, 1983).

### I.3.2 Cytological analysis of pancreatic material.

#### I.3.2.1 Cytological analysis of duodenal content.

When duodenal contents are analysed for the presence of malignant cells, great care should be taken to prevent deterioration of the material by lytic pancreatic enzymes. Addition of aprotinin and/or acid and immediate processing are advocated (Blanche Butler & Smithies, 1979). The sensitivity of this method for the detection of pancreatic cancer varies from 14% (Bourke, Swann et al, 1972) to 75% (Goldstein, Ventzke et al, 1968; Nundy, Shirley et al, 1974; Cooper, Moossa et al, 1978; Fitzgerald, Fortner et al, 1978; Mackie, Cooper et al, 1979). False positive results have been reported in 10% of the cases (DiMagno, Malagelada et al, 1977). The sensitivity of this procedure seems to be higher for tumors in the head of the pancreas than for tumors in the body or tail (Cooper, Moossa et al, 1978; Dreiling & Messer, 1978). In a number of instances no cells at all were obtained (Farini, Nitti et al, 1980).

#### I.3.2.2 Cytological analysis of pure pancreatic juice.

Cytological examination of pure pancreatic juice obtained by endoscopic cannulation of the papilla has been reported to give somewhat better results than analysis of duodenal contents with sensitivities varying from 54% (Hatfield, 1976) to 93% (Klapdor, Soehendra et al, 1980; Bodner, Schwanberg & Mikuz, 1982). The failure rate to obtain pure pancreatic juice was 44% in the latter study.

#### I.3.2.3 Fine needle aspiration biopsy of the pancreas.

Intraoperative needle aspiration biopsy of pancreatic tumors may help to differentiate between cancer and chronic pancreatitis. A correct diagnosis by this method was reported in 18/19 cases (Schick, Goldberg et al, 1980). In a much larger series, a correct diagnosis was reached in 89% (Bodner, Schwanberg & Mikuz, 1982).

Percutaneous needle biopsy of pancreatic tumors, guided by computer scan or ultrasonography, has been reviewed recently by Beazley (1981). Although the accuracy rate was found to be high and complications did not occur, the lack of cytopathologists prohibits widespread use of this method.

## I.3.3 Imaging procedures.

### I.3.3.1 Plain abdominal X-ray.

X-ray films of the upper abdomen without special preparation may demonstrate several signs of nonacute pancreatic disease.

Calcifications in the pancreas are pathognomonic of chronic calcifying pancreatitis and occur in about 60% of the patients with this disease (Guien, 1979). Occasionally, calcifications are demonstrated in pancreatic tumors (Nix, 1981). Differentiation between intra- and extrapancreatic calcifications may present difficulties in some cases.

Impression or displacement of air containing viscera, particularly the duodenum, by space occupying lesions of the pancreas.

Splenomegaly may occur in case of a tumor of the tail of the pancreas that gives rise to splenic vein thrombosis.

Dilatation of the gallbladder may be caused by obstruction of the common bile duct by a tumor in the head of the pancreas.

This procedure is relatively cheap and innocuous. It may provide important information but is of little value in the diagnosis of early chronic pancreatitis or early pancreatic cancer.

### I.3.3.2 Hypotonic duodenography.

Radiological examination of the duodenum after introduction of contrast through a transpyloric tube and induction of hypotony with drugs may outline those parts of the pancreas bordering the duodenum.

Increased width of the loop of the duodenum, which should not be more than the height of 2 vertebrae, indicates enlargement of the head of the gland (Guien, 1979). This may mean the presence of inflammation or tumor.

Displacement of the ligament of Treitz, that should be at level with the pylorus, points to a space occupying lesion of the tail of the pancreas.

Changes in the mucosal pattern on the inner aspect of the duonal loop are seen in pancreatitis and in pancreatic cancer (Guien, 1979).

Changes on hypotonic duodenography are seen in about 60-70% of the patients with chronic pancreatitis and pancreatic cancer (Arvanitakis, 1978). The accuracy of this procedure in diagnosing nonacute pancreatic pathology was found to be 85% (Nundy, Shirley et al, 1974). In icteric patients it was particularly the group of subjects with duodenal wall invasion by a tumor that was identified by hypotonic duodenography (Bourke, Swann et al, 1972). More recently, the accuracy of hypotonic duodenography in pancreatic disease was demonstrated

to be comparable to that of ultrasonography and computer scan, namely 80% (Redman, 1981). On the other hand, the latter procedures appeared more useful in identifying changes in neighbouring organs, e,g, the presence of liver metastases. Therefore, hypotonic duodenography has been generally abandoned in favor of these modern procedures.

I.3.3.3 Endoscopic retrograde cholangiopancreatography.

Intraoperative pancreatography has been practised since 1950, but since the arrival of the sideviewing duodenoscope in the 1970's retrograde pancreatography (E.R.C.P.) has become an established method of diagnosis of pancreatic disease (Cotton, 1979). Cannulation of the papilla is succesful in more than 90% of the cases in experienced hands (Kasugai, Kuno et al, 1972). It has been advocated that both the common bile duct and the pancreatic duct are visualised in every examination (Nix, 1981).

The risks of complication in this procedure are not negligible: even in expert hands acute pancreatitis and septic problems occur in 2-5% (Arvanitakis, 1978; Cotton, 1979). Administration of prophylactic antibiotics, both topically in the contrast medium and systematically, has been advocated. Damage of the ductal epithelium, raised serum amylase and lipase levels and impaired glucose tolerance after E.R.C.P. have been reported in man and in experimental animals (Stock & Riemann, 1981; Stolte, Bürner et al, 1981; Tulassay, Pap et al, 1981; Bub, Bürner et al, 1983).

Because of these risks it is generally accepted that E.R.C.P. should be performed only on strict indications and as a final step in the evaluation of pancreatic disease. The following indications are mentioned in the literature (Anacker, Weiss & Kramann, 1977; Rösch, 1979):

- suspicion of a tumor of the papilla or the pancreas while other examinations are normal or equivocal;
- suspicion of chronic pancreatitis while other examinations are normal or equivocal;
- to select the proper operative procedure in chronic pancreatitis, when the indication to operate has been made;
- the evaluation of pancreatogenic ascites;
- the evaluation of recurrent complaints after a drainage operation on the pancreas for chronic pancreatitis;
- Wirsungorrhagia, bleeding into the pancreatic duct;
- unexplained complaints after biliary tract surgery;
- the evaluation of extrahepatic biliary obstruction, when percutaneous transhepatic cholangiography has failed.

Rösch (1979) advocates the performance of E.R.C.P. as shortly as possible before a planned operation to prevent bacterial complications. This author also emphasises that a single attack of acute pancreatitis is not an indication for E.R.C.P., but others have found changes on pancreatography in acute pancreatitis that did alter the treatment plan (Hamilton, Bradley et al, 1982; Gebhardt, Riemann & Lux, 1983).

Contraindications to E.R.C.P. are:
- an inoperable patient;
- active pancreatitis (see above);
- active suppurative cholangitis, unless sphincterotomy is performed in the same session to drain the common bile duct (Aancker, Weiss & Kramann, 1977).

Endoscopic retrograde cholangiography will be discussed here only in as far as it has relevance for pancreatic pathology.

Pancreatography may tell whether 1) the pancreas is diseased 2) what kind of disease is present (tumor or inflammation), 3) what kind of operation is indicated (in chronic pancreatitis).

Furthermore, endoscopic cannulation of the pancreatic duct allows sampling of pure pancreatic juice for biochemical and cytological analysis.

I.3.3.3.1 E.R.C.P. in chronic pancreatitis.

The pancreatographic changes of chronic pancreatitis have been described by Kasugai and will be referred to as the Kasugai criteria (Kasugai, Kuno et al, 1972). See table I.9.

It is suggestive to see parallels between the changes on X-ray and the histological findings described in chronic pancreatitis, like dilatation and caliber irregularities of the main and small pancreatic ducts (Payan, Sarles et al, 1972; Nakamura, Sarles & Payan, 1972; Sarles & Sahel, 1976). However, the relationship between radiological and histological changes has not been studied systematically. A large number of surgical and autopsy specimens were apparently examined by Stolte but he mentions only scarce data (Stolte, 1979). He did find, for instance, a correlation between the diameter of the duct on E.R.C.P. and the histological stage of chronic pancreatitis (classified as mild, moderate or severe). Others have not been able to demonstrate this relationship between (radiologically defined) ductal diameter and histological severity (Adler, Waye & Dreiling, 1976; Grodzinsky, Schuman & Block, 1977). Despite these limitations, the pancreatogram is generally considered to reflect the anatomical changes that are inherent to the diagnosis 'chronic pancreatitis' according to the Marseilles' symposium definition (Sarles, 1965). An overall accuracy of E.R.C.P. in the diagnosis of chronic pancreatitis of

Table I.9 Criteria for the interpretation of the pancreatogram in chronic pancreatitis (Kasugai, Kuno et al, 1972).

| CHANGES | SEVERITY OF PANCREATITIS MINIMAL | MODERATE | ADVANCED |
|---|---|---|---|
| Main pancreatic duct | | | |
| Tortuosity | - | + | ++ |
| Dilatation & stenosis | - | + | ++ |
| Obstruction | - | - | + |
| Cyst formation | - | - | + |
| Calculi | - | - | + |
| Side branches | | | |
| Irregular distribution | + | ++ | +++ |
| Dilatation | + | ++ | +++ |
| Stenosis/obstruction | + | ++ | +++ |
| Cystic dilatation | - | + | ++ |
| Calculi | - | - | + |
| Acini | | | |
| Coarse opacification | - | - | + |
| Size of the pancreas | | | |
| Diminished | - | - | + |

94% has been reported in larger series (Stolte, 1979).

In the early stages of chronic pancreatitis, when changes occur mainly in the side branches, the diagnostic performance of E.R.C.P. is rather lower (Ashton, Axon & Lintott, 1978; Ruddell, 1981; Gowland, Kalantzis et al, 1981; Caletti, Brocchi et al, 1982; Ruddell, Lintott & Axon, 1983). In a retrospective analysis of 100 E.R.C.P. films by 4 radiologists, it appeared that only in those cases where the diagnosis was evident before the E.R.C.P. was done, the opinions of the radiologists coincided; in less clear-cut cases the differences of opinion amounted to 50% (Gaucher, Bigard et al, 1981). Similar data have been published by others (Stolte, 1979; Cotton, 1979)

Stenosis of the common bile duct in chronic pancreatitis has been reported by several authors (Siegel, 1979; Warshaw, Rattner et al, 1980). Therefore, the common bile duct should always be visualised in E.R.C.P. examinations, even when no abnormalities are expected Nix, 1981).

I.3.3.3.2 E.R.C.P. in pancreatic cancer.

According to Stolte, 4 types of changes may be demonstrated by E.R.C.P. in pancreatic cancer (Stolte, 1979):
- obstruction of the main duct;
- stenosis of the main duct, both with distal dilatation;
- irregular cystic dilatation, due to necrosis of the tumor;
- tapering of the main duct.

In itself, these changes are not considered specific for pancreatic cancer as they may also occur in chronic pancreatitis (Cotton, 1979). The differentiation between pancreatitis and tumor may be facilitated by calculation of the ratio between the diameters of side branches and main duct (Nix, 1981).

The diagnostic accuracy of E.R.C.P. in pancreatic cancer is 90% and more in various papers (Anacker, Weiss & Kramann, 1977; Foley, Stewart et al, 1980; Freeny & Ball, 1981; Frick, Feinberg & Goodale, 1982). This figure might be further improved by combining the procedure with cytological analysis of pure pancreatic juice (Hatfield, 1976; Klapdor, Soehendra et al, 1980).

Although E.R.C.P. can demonstrate fairly accurately the presence of a tumor, it does not provide information on extra-pancreatic spread (Cotton, 1979). Furthermore, peripheral tumors, that do not arise in the ductal epithelium, like endocrine neoplasms, may be missed by E.R.C.P. (Cotton, 1979).

In summary, E.R.C.P. is a highly specialised procedure, requiring skilled endoscopists and radiologists. Even in their hands, cannulation of the duct fails in about 10%. The risks to the patients are not negligible. On the other hand, E.R.C.P. may provide information that can be obtained in no other way.

I.3.3.4 Computed tomography.

The introduction of computed tomography in 1972 has made the pancreas much more accessible without significant risk to the patient. Changes in size, shape and density can be made visible with a radiation exposure that is equal to 1 minute of fluoroscopy, which is one third the exposure of a barium enema or intravenous urography (Gore, Moss & Margulis, 1982). A disadvantage of computed tomography is the high capital investment for the apparatus.

In chronic pancreatitis, computed tomography may demonstrate calculi, dilatation of the duct and pseudocysts, but early changes of density and shape are more difficult to visualise (Isherwood & Fawcitt, 1979).

Tumors with a diameter of 2 cm. and more are generally clearly identified, while smaller tumors may be detected by indirect evidence, like dilatation of the main pancreatic or

common bile duct. The overall accuracy of computed tomography in pancreatic cancer is 88-94% (Isherwood & Fawcitt, 1979). This procedure provides not only information about the presence of a pancreatic tumor but also about its relation to neighbouring structures. Thus, it may save some patients an unnecessary laparotomy by demonstrating irresectability (Goldberg, Glazer & Axel, 1981; Freeny & Ball, 1981; Gore, Moss & Margulis, 1982). Furthermore, computed tomography may guide percutaneous needle biopsy of a mass in the pancreas (Gore, Moss & Margulis, 1982).

The diagnostic performance of computed tomography in the analysis of patients with noncharacteristic abdominal complaints was recently reviewed (Kolmannskog, Vatn et al, 1983). It appeared that computed tomography provided relevant information only in those patients in whom less sophisticated procedures had already indicated the presence of organic disease. Therefore, it was advised not to use computed tomography as a screening test.

### I.3.3.5 Radioisotope scan.

Because of the high rate of protein metabolism of the pancreas, $^{75}$Se-selenomethionine will be concentrated in the gland. One hour after intravenous administration of the isotope, radioactivity is measurable with external scanning techniques. This procedure provides information on 2 aspects of the pancreas: the protein synthesis rate, which is a function of the acinar cells, and the structure of the gland. In several reports the sensitivity of this examination for pancreatic disease appeared to be 90-95%, but differentiation between chronic pancreatitis and pancreatic cancer was not possible in most cases; the specificity was only 60-70% Testa, 1979). The procedure has been advocated as a screening technique at a time when other imaging methods, like ultrasonography and computed tomography, were not yet widely available (Nundy, Shirleyet al, 1974). Recent modifications of radioisotope scanning include estimation (of the excretion) of the isotope in duodenal contents (Pointner & Kletter, 1980; Boyd, Wood et al, 1983) and the use of another isotope, $^{11}$C-L-methionine (Syrota, Dop-Ngassa et al, 1981). See also section I.3.1.1.3.

### I.3.3.6 Angiography.

Selective and superselective cannulation of the coeliac and superior mesenteric artery and their branches may produce important information about the diseased pancreas. It is a technique that requires much skill of the radiologist and that carries some risk to the patient because of its invasive character.

In chronic pancreatitis several specific arteriographic findings have been described, like progressive narrowing of the larger arteries, beading of the arterioles and aneurysm formation. Nonspecific changes include notching, cuffed stenosis and angulation of the vessels (Guien, 1979). Although angiography will usually not be performed to obtain a diagnosis in chronic pancreatitis, it may be important to distinguish these features from those seen in cancer (Forell, 1979; Anacker, Weiss & Kramann, 1977).

Characteristic angiographic changes in pancreatic cancer are: short and irregular stenosis of the larger trunks, toothing, truncation and serpiginous appearance of the arterioles (Guien, 1979). Involvement of the larger arteries and veins often means that the tumor is irresectable (Moossa & Levin, 1981; Obertop, Bruining et al, 1982). The diagnostic accuracy of angiography in pancreatic cancer is 80-95% (Fitzgerald, Fortner et al, 1978; Arvanitakis, 1978; Moossa & Levin, 1981; Rosch & Keller, 1981).

Except for its properties in the diagnosis of pancreatic disease, angiography is also indicated in order to evaluate the vascular anatomy of the pancreas before major resections are performed. This evaluation is important because anatomical variations do occur whereby the (right) hepatic artery originates from the superior mesenteric artery (Anson & McVay, 1971).Also, arteriosclerotic obstructions may have blocked more of the large arterial trunks, in which case the pancreaticoduodenal arcades provide collateral circulation of the liver and/or gut (Thompson, Eckhauser et al, 1981). In both instances, severe impairment of the circulation of the abdominal organs may result from pancreatic resections if this situation is not appreciated (Thompson, Eckhauser et al, 1981).

### I.3.3.7 Ultrasonography.

By ultrasonography changes in size and consistency of the pancreas may be discovered. In chronic pancreatitis the size of the gland may be increased in the early cases or in acute exacerbations, but is more often reduced with an increase in consistency because of sclerosis. It is also possible to measure the diameter of the pancreatic duct by ultrasonography, particularly when it is dilated. Pseudocysts are usually well recognised by ultrasonography as are tumors with a diameter of more than 2 cm.(Pietri & Sahel, 1979). Neighbouring strucures, like gallbladder, common bile duct and liver can also be made visible by this technique in the same session. Cytological needle biopsy of a tumor may be guided by ultrasonography.

Obesity and bowel distension impair the quality of the examination. The diagnostic accuracy depends also on the skill and experience of the examiner and varies between 67 and 91%

for pancreatic disease in several studies (Fitzgerald, Fortner et al, 1978; Foley, Stewart et al, 1980; Gowland, Kalantzis et al, 1981; Pollock & Taylor, 1981).
The failure rate, that is the proportion of unsatisfactory examinations, amounts to 25% in some papers (Gowland, Kalantzis et al, 1981; Bernardino & Barnes, 1982)

The noninvasive character and the absence of risks to the patient, together with a reported overall accuracy of about 80% appear to make ultrasonography the procedure of first choice in the investigation of patients with suspected pancreatic disease.

Recently, a promising report has appeared on endoscopic ultrasonography, which allows identification of structures smaller than 1 cm. diameter (DiMagno, Regan et al, 1982).

### I.3.3.8 Intravenous cholangiography.

Abnormalities of the common bile duct are seen in up to 60% of the patients with chronic pancreatitis (Guien, 1979; Siegel, Sable et al, 1979). In pancreatic cancer obstructive jaundice occurs due to compression of the common bile duct. In jaundiced patients, intravenous cholangiography is usually not possible and percutaneous transhepatic cholangiography or E.R.C.P. will be needed to elucidate the anatomical situation. Therefore, the role of intravenous cholangiography in the diagnosis of pancreatic disease is limited (Goodman, Ansel et al, 1980).

### I.3.3.9 Laparoscopy and biopsy of the pancreas.

Recently, two reports have been published on the use of laparoscopy (with an incision in the lesser omentum to inspect the pancreas) combined with aspiration biopsy in the diagnosis of pancreatic disease (Ishida, Furukawa et al, 1981; Boyd, Wood et al, 1982).

## I.3.4 Evaluation of various diagnostic procedures.

In a recent article a radiologist explains the preser malaise surrounding radiologic diagnosis at a time of grea accomplishments in the development of imaging techniques an blames radiologists for "allowing themselves virtually n control over the ordering and sequencing of the examination they perform..." Thus "the clinician enters the radiologi supermarket whose shelves are increasingly filled with exoti and expensive studies, and orders tests at will..." (Heilman 1982). In the previous section a review has been given of a number of functional and imaging diagnostic procedures available for the investigation of the patient suspected to have pancreatic disease. Although it has been emphasised that the majority of the studies are not comparable because of methodological differences, patient selection and such factors, it should be possible to create some kind of order in this multitude of tests and examinations. In this section an attempt will be made to compare various procedures and to outline specific advantages and limitations.

The secretin-CCK test and other function tests.

The secretin-CCK test is a modification of the oldest pancreatic function test and is considered as the standard with which newer test are compared.

The Lundh test, based on endogenous stimulation of the exocrine pancreas with a testmeal, appears to have hardly any advantages over the secretin-CCK test, while it has several disadvantages, like the influence of extrapancreatic factors on the test result. In clinical practice the diagnostic performance of the Lundh test is probably less than that of the secretin-CCK test, particularly in less advanced stages of pancreatic disease. See I.3.1.1.1.1

The so called noninvasive tests of pancreatic exocrine function have the advantage that duodenal intubation is avoided. In several studies an apparently good correlation between the P.A.B.A. recovery rate in the urine and one or more parameters of the secretin-CCK test was demonstrated (Arvanitakis, 1978; Imamura, Nakamura et al, 1978; Cavallini, Piubello et al, 1980; Kimura, Wakasugi & Ibayashi, 1981).The overlap between controls and patients with chronic pancreatitis, however, is quite large in most of these reports, thus the clinical relevance appears limited, particularly in less advanced cases. The Lundh test has also been shown to be superior to the P.A.B.A. test. (Gyr, Stalder et al, 1976; Delchier & Soule, 1983).

In a recent editorial on noninvasive exocrine pancreatic function test DiMagno concluded that invasive tests requiring duodenal intubation followed by exogenous stimulation continue to be the standard (DiMagno, 1982[b]). The relevance of the

noninvasive tests at the present time appears to be limited to the differentiation between pancreatogenic steatorrhoea and other malabsorption syndromes (Toskes, 1983).

The secretin-CCK test and E.R.C.P. in chronic pancreatitis.

Studies comparing the secretin-CCK test with E.R.C.P. in the diagnosis of chronic pancreatitis are summarised in table I.10. It should be stressed that numerous methodological differences, regarding both the secretin-CCK test and the (interpretation of the) E.R.C.P., make it difficult to draw conclusions.

Several authors have taken the diameters of the main duct as criterium for the interpretation of E.R.C.P.. Nakano and coworkers found a positive correlation between diameter of the main duct on E.R.C.P. and severity of secretin-CCK test impairment in chronic pancreatitis (Nakano, Nakajima et al, 1974), but in patients with suspected chronic pancreatitis this correlation was not present (Nakajima, Nakano et al, 1976). Similarly, Otte (Otte, 1979) found a positive correlation betwee ductal diameter and secretin-CCK test results in advanced but not in early chronic pancreatitis.

When Kasugai criteria (see table I.9) are applied to the E.R.C.P. films, the correlation with the results of the secretin -CCK test appears statiscally significant mainly in patients with advanced chronic pancreatitis (Adler, Waye & Dreiling, 1976; Dobrilla, Fratton et al, 1976; Tympner, Schaffner et al, 1979; Rolny, 1980; Tittobello, Testoni et al, 1980; Valentini, Cavallini et al, 1981). Thus the compatibility rate in chronic pancreatitis of E.R.C.P. and secretin-CCK test is about 75%.

Table I.10 Comparison of secretin-CCK test and E.R.C.P. in chronic pancreatitis in the literature.

| Author, year | Number of patients[1)] | E.R.C.P. criterium | Percentage compatible[1)] |
|---|---|---|---|
| Adler, '76 | 24 | Kasugai | 54 |
| Dobrilla,'76 | 17 | Kasugai | 79 |
| Nakano,'74 | 21 | Diameter duct | 75 |
| Otte, '79 | 122 | Duct changes | 72 |
| Rolny,'80 | 23 | Duct changes | 78 |
| Salmon,'75 | 29 | Kasugai | 65 |
| Tittobello,'80 | 14 | Kasugai | 79 |
| Tympner,'79 | 87 | Kasugai | 91 |
| Valentini,'81 | 65 | Kasugai | 79 |

1) These figures relate to the patients with chronic pancreatitis in whom E.R.C.P. and secretin-CCK test results were compatible

An interesting statistical analysis was performed by Kasugai and coworkers, who calculated regression equations of secretin-CCK test parameters on E.R.C.P. grade (Oguri, Kasugai & Kuno, 1976). Their results indicate that the secretin-CCK test and E.R.C.P. are complementary in the diagnosis of chronic pancreatitis because function and structure are two separate aspects. Similar results were obtained by Braganza and her group (Braganza, Hunt & Warwick, 1982). The authors argue that this might be explained by the patchy nature of chronic pancreatitis ('the lobular distribution' see I.2.1.2.2). Other possible explanations for the inconsistent correlations between structural and functional changes in chronic pancreatitis are: compensatory hypertrophy of the intact parenchyma, and increased sensitivity of the acinar tissue to stimulating influences (Braganza, Hunt & Warwick, 1982).

In summary, it appears that, when E.R.C.P. is interpreted according to the criteria of Kasugai, the early ductular changes in chronic pancreatitis do not necessarily coincide with impairment of exocrine pancreatic function as measured by the secretin-CCK test. In moderate and advanced cases, E.R.C.P. and secretin-CCK test are usually compatible. In pancreatic cancer, the relationship between E.R.C.P. and the secretin-CCK test has not been explored in sufficiently large series of patients to allow any conclusions.

E.R.C.P. and other imaging techniques.

Compared to computed tomography, E.R.C.P. was found to be less reliable in the diagnosis of chronic pancreatitis (68% and 90% accuracy respectively) but more reliable in the diagnosis of pancreatic cancer (100% and 71% accuracy respectively (Foley, Stewart et al, 1980). Others have found E.R.C.P. to be superior to computed tomography and ultasonography in the diagnosis of both chronic pancreatitis and pancreatic cancer (Cotton, 1979). Nevertheless, computed tomography was found to have reduced the number of E.R.C.P. examinations performed (Freeny & Ball, 1981). These and other authors advise E.R.C.P. for the evaluation of cases in which computed tomography is equivocal or technically unsatisfactory (Freeny & Ball, 1981; Frick, Feinberg & Goodale, 1982).

Similarly, computed tomography has also modified the indications for selective angiography as a staging procedure in pancreatic cancer (Stanley, Sagel & Evans, 1980).

In one report ultrasonography was found to be more accurate than E.R.C.P. in the diagnosis of chronic pancreatitis and as accurate as E.R.C.P. and angiography in the diagnosis of pancreatic cancer (Pietri & Sahel, 1979).

In summary, it appears that E.R.C.P., computed tomography and selective angiography are useful in the diagnosis of nonacute pancreatic disease only when other examinations have demonstrated the presence of pancreatic pathology. First line procedures for the investigations of suspected pancreatic disease should be cheap, relatively easy to perform, harmless to the patient and highly sensitive, but not necessarily very specific. Ultrasonography appears to meet several of these requirements but it has an unacceptably high failure rate in visualising the whole pancreas, namely 25% in some reports. The secretin-CCK test also fulfills most of these conditions, but it appears to have been abandoned more and more in favour of the imaging techniques and of the noninvasive tests. This might be due to the many methodological variations of the secretin-CCK test and to the fact that the relationship between exocrine function and morphological changes in chronic pancreatitis is not well established.

Therefore, it appears justified to reevaluate the secretin-CCK test in the light of the new imaging techniques and to examine its relationship with morphological changes in chronic pancreatitis.

# II PRESENT STUDY

## II.1 Outline of the study.

With the aim of reevaluating the secretin-CCK test in the light of the new imaging techniques, we analysed retrospectively the data of 299 patients in whom the test was performed between September 1975 and February 1982.

All patients tested were attending the departments of Internal Medicine or General Surgery of the University Hospital Dijkzigt, Rotterdam and the tests were performed in the investigation for clinical signs and symptoms suspect of pancreatic pathology. The data analysed in this study therefore comprise the secretin-CCK test results and details from the patients records concerning various diagnostic and therapeutic (radiological, endoscopical and surgical) procedures that had led to the diagnosis made by the clinicians in charge of the patient.

The results of the review of the patients' records will be presented in chapter II.2 together with a classification of patients into several groups according to the diagnosis.

In chapter II.3 the data of the secretin-CCK tests will be analysed. First, mean and standard deviation of the parameters are presented for each diagnostic group. This is followed by an analysis of the reproducibility of the test and of the recovery rate of the sampling method of duodenal contents. Subsequently, the problem of interpretation of the test data will be dealt with. Discriminant analysis has been used for this purpose. After having chosen the criteria that distinguish between normal and abnormal test results, the diagnostic performance of the test will be assessed in the same patients. Finally, the results will be discussed for the various diagnostic groups, for diabetic patients and for patients after gastric surgery.

The results of faecal chymotrypsin estimations in our patients are presented in chapter II.4, and compared with the results of the secretin-CCK test.

In chapter II.5 the E.R.C.P. data of 75 patients of whom full details were avauilable are analysed and correlated with the secretin-CCK test data, with the aim of exploring the relationship between the exocrine pancreatic function and morphological changes in pancreatic disease.

Similarly, in chapter II.6, the relationship between secretin n-CCK test data and histological findings of 25 patients with chronic pancreatitis who came to surgery is analysed.

Each of these 5 chapters is concluded by an evaluation of the results. Finally, a general discussion is presented as part III in which the results are related to the data from the literature and in which answers are sought to the questions posed in the Introduction.

## II.2 PATIENTS, SELECTION AND CLINICAL DIAGNOSIS.

### II.2.1 Radiological examinations performed.

A review of the radiological examinations performed in 299 patients during the clincal investigation for their signs and symptoms is presented in table II.2.1. Plain X-ray of the abdomen was done in most patients (93%) and ultrasonography in 75%. Hypotonic duodenography and E.R.C.P. were each done in less than half of the patients, while computed tomography and angiography were performed only in a minority of the cases. Also shown in the table are the failure rates of ultrasonography and E.R.C.P., 20% and 14% respectively.

Table II.2.1

| Examination | Number performed | Percentage performed | Failure rate(%) |
|---|---|---|---|
| Plain X-ray | 279 | 93 | |
| Hypotonic duodenography | 120 | 40 | |
| Ultrasonography | 225 | 75 | 20 |
| E.R.C.P. | 96 | 32 | 14 |
| Computed tomography | 34 | 11 | |
| Angiography | 20 | 7 | |

Table II.2.2 General characteristics of 299 patients in whom the secretin-CCK test was performed.

| Group | Size | Percentage males | Mean age | Percentage alcoholics | Percentage diabetics |
|---|---|---|---|---|---|
| 1 | 25 | 76 | 44 | 83 | 39 |
| 2 | 38 | 82 | 45 | 71 | 32 |
| 3 | 34 | 62 | 43 | 72 | 12 |
| 4 | 11 | 55 | 60 | 33 | 18 |
| 5 | 2 | 100 | 22 | -- | -- |
| 6 | 120 | 71 | 44 | 30 | 8 |
| 7 | 69 | 70 | 42 | 25 | 3 |

1 = histological proof of chronic pancreatitis
2 = chronic pancreatitis, clinical diagnosis
3 = suspected chronic pancreatitis
4 = tumor of the pancreas
5 = cystic fibrosis
6 = other diagnosis
7 = no organic disease

II.2.2. Clinical data and classification of patients.

With the details retrieved from the patients' records, a classification was made according to diagnosis into 7 groups, see table II.2.2.

Histological proof of chronic pancreatitis was available of 25 patients, who were assigned to group 1. Details of the histological findings will be discussed in chapter II.6.

Group 2 consisted of 38 patients in whom the diagnosis chronic pancreatitis was made on clinical and radiological grounds: 13 had calcifications on the plain X-ray, while E.R.C.P. findings demonstrated changes compatible with chronic pancreatitis in 25 more patients.

Thus, altogether 63 patients with the diagnosis chronic pancreatitis were tested, 38% of them had calcifications on the plain X-ray, 35% had diabetes, 25% had steatorrhoea and 40% was submitted to surgery. The aetiological factors are listed in table II.2.3

Table II.2.3. Aetiological factors in 63 patients with chronic pancreatitis.

| Etiology | Group 1 Number | (%) | Group 2 Number | (%) | Total Number | (%) |
|---|---|---|---|---|---|---|
| Alcohol | 19 | (76) | 27 | (71) | 46 | (73) |
| Idiopathic/unknown | 4 | (16) | 9 | (24) | 13 | (21) |
| Hereditary | - | | 1 | | 1 | |
| Drugs | 1 | | 1 | | 2 | |
| Tropical form | 1 | | - | | 1 | |
| Total | 25 | | 38 | | 63 | |

Alcohol abuse was noted in 73% of the patients. In 21% no cause could be identified. In the remaining four patients various other factors were present: one patient belonged to a family with hereditary pancreatitis, two patients had taken drugs that are known to be associated with chronic pancreatitis, namely corticosteroids in one case (for chronic astma) and valproic acid (for epilepsy) in the other; one young Hindustani woman from Surinam, who did not drink alcohol nor took any drugs, was thought to have the tropical form of chronic pancreatitis.

Group 3 consisted of 34 patients in whom chronic pancreatitis was suspected on clinical and radiological grounds. As the results of the analysis in these patients were either incomplete or equivocal or even contradictory, they were considered separately. A majority of the patients in this group had

clinical symptoms that were not severe enough to warrant invasive diagnostic procedures, like E.R.C.P. This group 3 also contained four patients with painless exocrine pancreatic insufficiency. None of these patients was alcoholic and only one had mild diabetes mellitus. Two of them were females and three were younger than 20 years of age. E.R.C.P. in these patients showed a gracile duct with fine irregularities of the wall but no signs of chronic pancreatitis. See also chapter II.5.

Eleven patients with a tumor of the pancreas were assigned to group 4. The mean age of these patients was considerably higher than in the other groups. Alcohol abuse was less frequent than in patients with chronic pancreatitis. Surgery was performed in all but one patient and only one patient appeared to have a resctable tumor. In one patient secondary deposits of a breast cancer to the pancreas were diagnosed: E.R.C.P. demonstrated a lesion in the periphery of the gland, unlike the picture in pancreatic duct cell carcinoma. Further details of the patients with a tumor are given in table II.2.4.

Table II.2.4 Details of 11 patients with a tumor of the pancreas.

| Patient | Histology | Localisation | Treatment |
|---|---|---|---|
| A | Adenoca. | Head | Irresectable |
| B | Adenoca. | Body | Irresectable |
| C | Islet cell tumor + chron.pancreatitis | Tail | Resected |
| D | Adenoca. | Head | Irresectable |
| E | Islet cell tumor | Head + body | Irresectable |
| F | Adenoca. | Body | Irresectable |
| G | Adenoca. | Head | Irresectable |
| H | Adenoca. | Head | Irresectable |
| I | Not available | Body | Not operated (2° deposit) |
| J | Adenoca. | Head | Irresectable |
| K | Adenoca. | Head | Irresectable |

Two patients with cystic fibrosis were tested, both young men with longstanding disease. The diagnosis had been confirmed by several procedures, among which the sweat test. They formed the 5th group.

In group 6 120 patients with various other diagnoses were assembled. Table II.2.5 lists the various diagnoses made in these patients. Among them were 15 patients with previous episode(s) of acute pancreatitis.

In group 7 were included 69 patients in whom no organic disease was found, often after extensive investigations.

Table II.2.5 Diagnosis made in patients of group 6.

| Diagnosis | Size of patient group: Nonalcoholics | Alcoholics | Total |
|---|---|---|---|
| Hiatal hernia | 10* | 3* | 13 |
| Oesophageal varices | 1* | - | 1 |
| Gastritis | 18* | 2 | 20 |
| Gastric ulcer | 2 | - | 2 |
| Duodenitis | 3 | 2* | 5 |
| Duodenal ulcer | 6* | 6 | 12 |
| Gallstones | 2 | 4 | 6 |
| Other biliary pathology | 4* | - | 4 |
| Liver cirrhosis/steatosis | - | 5 | 5 |
| Chronic hepatitis | - | 2 | 7 |
| Prim.biliary cirrhosis | 2 | - | 2 |
| Crohn's disease | 4 | - | 4 |
| Other small bowel disease | 5 | 1 | 6 |
| Large bowel disease | 6 | 2 | 8 |
| Diabetes (main diagnosis) | 2* | 1 | 3 |
| Other endocrine diseases | 2 | - | 2 |
| Carcinoma of lung | 1* | 1 | 2 |
| ovary | 1 | - | 1 |
| breast | 1 | - | 1 |
| Acute pancreatitis | 8 | 7 | 15 |
| Other diseases | 8 | 1 | 9 |
| Total | 84[1)] | 36[1)] | 120[1)] |

1) In several patients* more than one diagnosis was recorded.

II.2.3. Evaluation of patient material.

The diagnosis made by the physician or surgeon treating the patient, which was based on clinical, radiological and histological evidence, was used to classify patients into 7 groups. This classification was required for the evaluation of the secretin-CCK test.

Chronic pancreatitis was diagnosed in 63 patients, 25 of whom had been submitted to pancreatic surgery. The percentage of patients with calcifications, diabetes and steatorrhoea is comparable to that in the literature, see table I.7. Most of these patients were alcoholics but several other etiological factors were encountered: hereditary pancreatitis, drugs and tropical pancreatitis.

The diagnosis chronic pancreatitis depends on the criteria used (see chapter I.3.1.2.4). In our patients in group 1 and 2 the following criteria were maintained:

- histology positive in 25 patients
- calcifications present in 13 patients
- E.R.C.P. abnormal in 25 patients

**The secretin-CCK test was not used for the diagnosis or classification of the patients.**

In 34 patients (group 3) signs and symptoms suggested chronic pancreatitis but the investigations had been incomplete and the diagnosis could not be confirmed, usually because the relatively mild clinical course did not justify invasive procedures. It is interesting to note that the general characteristics of these patients, as presented in table II.2.2., are more comparable to those of the patients with proven chronic pancreatitis than to those of patients with other diagnoses or patients without organic disease. It is therefore not unlikely that among these patients with suspected chronic pancreatitis, there were a number of cases with early disease. At any rate, the classification of these patients as a separate group appears justified. This group also included 4 young patients with painless exocrine pancreatic insufficiency. The E.R.C.P. changes in these patients were similar to the changes seen in pancreatic lipomatosis (Stolte, 1979), a syndrome that has been reported to occur mainly in elderly people. Pancreatic tissue was not available for histological examination in our patients. All patients with a tumor of the pancreas (group 4) in whom the secretin-CCK test was performed appeared to have advanced lesions: resection was possible in only one patient with an islet cell tumor. Alcohol abuse was not as frequent in this group of patients as in the groups of patients with chronic pancreatitis, which is in line with the opinion that alcohol has no etiological role in pancreatic cancer (McMahon, 1982). One patient was thought to have secondary deposits from a breast tumor to the pancreas (see chapter I.2.3.2).

Patients with diagnoses other than nonacute pancreatic disease: chronic pancreatitis, pancreatic cancer or cystic fibrosis, were included in group 6. The 15 patients with acute pancreatitis were also assigned to this group, as these patients were not expected to have exocrine function impairment (see chapter I.2.1.1).

Patients in whom no organic disease was found were collected in group 7 with the aim of using this group as control group, as all patients had signs or symptoms imitating pancreatic disease but no objective evidence had been found, often after extensive analysis.This distinguishes group 7 from group 3, in which in each case some evidence of pancreatic disease was found but insufficient to warrant the diagnosis chronic pancreatitis.

**Such a group of patients is a better control group than a group of healthy volunteers, because in clinical practice tests are never required to identify healthy volunteers.**

A variety of radiological examinations had been performed in the clinical investigation of our patients. Table II.2.6 presents the frequency with which each procedure was performed in each diagnostic group and the frequency of changes indicating nonacute pancreatic disease for each procedure.

Plain films of the abdomen were performed in most patients and calcifications were demonstrated in 38% of the patients with chronic pancreatitis and in 18% of the patients with a tumor of the pancreas.

Hypotonic duodenography was performed in 40% of the patients. The results, as noted in the patients' records, indicated the presence of pancreatic disease in a fairly high proportion of patients, also in those patients in whom other procedures failed to find any abnormality. This means a high false positive rate.

Ultrasonography was done in 75% of the patients but it was helpful only in patients with a tumor of the pancreas in a substantial number of cases. In the other groups the failure rate was fairly high (see also table II.2.8).

E.R.C.P. was attempted in a majority of patients with chronic pancreatitis and tumor of the pancreas. Particularly in this latter group, a large proportion of the cannulations failed.

Computed tomography and selective angiography were performed in a small number of patients, each with a high yield of positive findings. Computed tomography became available only late during the period of observation, which explains the small number of patients in whom this procedure was performed.

Table II.2.7 presents the diagnostic performance, as assessed by calculation of sensitivity and specificity, of the radiological examinations used in this study. It should be emphasised that these examinations were used for the diagnosis and classification of the patients. **Therefore, the diagnostic performance of these procedures will be favourably biased.** For example, calcifications on the plain X-ray are considered pathognomonic for chronic pancreatitis and all patients with calcifications are included in groups 1 and 2. Thus, the specificity of the plain X-ray is 100%. To a certain extent, the same is true for the E.R.C.P. On the other hand, hypotonic duodenography was never used as a single criterium for pancreatic disease. Ultrasonography was introduced during the period of observation and expertise gradually increased. Nevertheless, a 'normal' ultrasonography result was not considered prove of the absence of pancreatic disease. This is demonstrated by a low sensitivity which limits its application as a screeing test for pancreatic disease.

Another item of interest is the relatively high failure rate of ultrasonography (20% for all cases) and of E.R.C.P. (14% for all cases). The failure rate for E.R.C.P. was notably high in

the patients with a tumor of the pancreas: 50%. This might be explained by obstruction of the papilla and pancreatic duct in these, mainly advanced cases (table II.2.8).

Table II.2.6 Radiological examinations performed in 7 diagnostic groups

| Group | 1 | 2 | 3 | 4 | 6 | 7 | Total |
|---|---|---|---|---|---|---|---|
| Size of group | 25 | 38 | 34 | 11 | 120 | 69 | 299 |
| Plain X-ray | | | | | | | |
| Number performed | 24 | 37 | 31 | 11 | 107 | 69 | 279 |
| % Abnormal | 42 | 35 | - | 18 | - | - | |
| Hypotonic | | | | | | | |
| Number performed | 14 | 14 | 13 | 5 | 46 | 28 | 120 |
| % Abnormal | 50 | 57 | 85 | 60 | 48 | 32 | |
| Ultrasonography | | | | | | | |
| Number performed | 19 | 30 | 29 | 9 | 84 | 54 | 225 |
| % Abnormal | 32 | 23 | 24 | 89 | 20 | 9 | |
| E.R.C.P. | | | | | | | |
| Number performed | 18 | 27 | 12 | 5 | 24 | 10 | 96 |
| %Abnormal | 100 | 96 | 67 | 100 | 29 | - | |
| Computed tomography | | | | | | | |
| Number performed | 6 | 5 | 4 | 3 | 7 | 9 | 34 |
| % Abnormal | 100 | 80 | 100 | 100 | 14 | 22 | |
| Angiography | | | | | | | |
| Number performed | 6 | 2 | 4 | 7 | 1 | - | 20 |
| % Abnormal | 100 | 100 | 75 | 100 | 100 | - | |

Table II.2.7 Diagnostic performance of various radiological examinations.

| Examination | Patients with chronic pancreatitis: number performed | Patients with chronic pancreatitis: percentage abnormal = sensitivity | Patients without pancreatic disease: number performed | Patients without pancreatic disease: percentage normal = specificity |
|---|---|---|---|---|
| Plain X-ray | 61 | 38 | 175 | 100 |
| Hypotonic | 28 | 54 | 74 | 58 |
| Ultrasonography | 49 | 26 | 138 | 84 |
| E.R.C.P. | 45 | 98 | 34 | 79 |
| Computed tomography | 11 | 91 | 16 | 81 |

Table II.2.8 Failure rate of E.R.C.P. and Ultrasonography in each group

| Group | Ultrasonography: Number attempted | Ultrasonography: Percentage failed | E.R.C.P.: Number attempted | E.R.C.P.: Percentage failed |
|---|---|---|---|---|
| 1 | 19 | 26 | 23 | 22 |
| 2 | 30 | 20 | 27 | - |
| 3 | 29 | 24 | 15 | 20 |
| 4 | 9 | - | 10 | 50 |
| 6 | 84 | 18 | 25 | 4 |
| 7 | 54 | 15 | 12 | 17 |
| Mean | | 20 | | 14 |

## II.3 THE SECRETIN-CHOLECYSTOKININ TEST

### II.3.1 Methods

#### II.3.1.1 Test procedure

The secretin-CCK test was performed both on inpatients and on outpatients. All tests were done in the morning hours after an overnight fast. Patients were not submitted to the test when there were signs of an acute attack (relapse or exacerbation) of pancreatitis.

Duodenal contents, uncontaminated by gastric contents, was collected via a double lumen Dreiling tube. This tube consists of a gastric part with a length of 60 cm. and a duodenal part with a length of 90 cm. The distal tip of the tube consists of a metal olive to facilitate passage through the pylorus. As a rule, no diffculties were encountered in positioning the distal tip near the ligament of Treitz under fluoroscopic control. Constant suction of 0.5 atm. was applied to each lumen, the gastric aspirate was discarded and the duodenal material collected in bottles placed in melting ice, in 15 min. portions.

After an initial stabilising period of 15 minutes, the basal period, stimulation of the exocrine pancreas was started. An intravenous drip was set up in order to administer: SECRETIN GIH (Karolinska Institute, Stockholm), 0.25 CU/kg/hour and CHOLECYSTOKININ GIH, 1 IDU/kg/hour, simultaneously for a period of 105 minutes. Thus, 7 portions of duodenal contents were sampled during stimulation. During the period of observation, natural GIH cholecystokinin was replaced by synthetic CCK-octapeptide, sincalide (Kinevac$^{R}$, Squibb) in a dose of 40 ng/kg /hour. This dose has been shown to be equipotent to 1 IDU of natural GIH cholecystokinin (see also table I.4).

The 8 samples obtained (1 basal and 7 after stimulation) were measured in a calibrated container for volume and the pH was estimated with indicator strips. Bicarbonate concentration was estimated by the enzymatic method according to the instructions of the Dupont ACA apparatus and expressed as mmol/l. When the pH was found to be below 7, bicarbonate powder was added to the aliquot for chymotrypsin estimation to prevent inactivation of the enzyme. Chymotrypsin activity was estimated with n-acetyl-tyrosin-ethyl-ester (A.T.E.E.) as substrate and expressed as U/ml. (Ammann, 1967). A scheme of the test procedure is presented in Figure II.3.1.

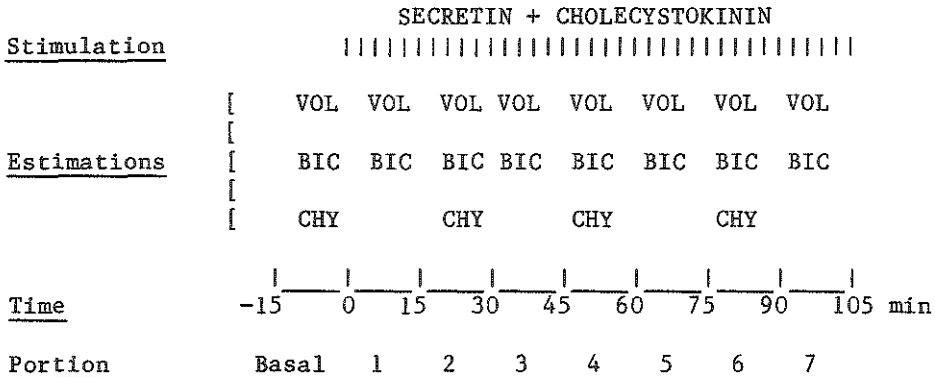



Figure II.3.1. Scheme of secretin-CCK test.

VOL = volume, ml
BIC = bicarbonate, mmol/l
CHY = chymotrypsin, U/ml

Thus, a set of data was obtained for each test , representing volume (8 portions), bicarbonate concentration (8 portions) and chymotrypsin concentration (4 portions). From these values, bicarbonate and chymotrypsin output were calculated for each portion by multiplying volume and concentration. In this way, 5 parameters could be discerned: VOLUME, BICARBONATE CONCENTRATION, BICARBONATE OUTPUT, CHYMOTRYPSIN CONCENTRATION

For each of these 5 parameters, basal, peak, mean and total values were calculated and used for further analysis. See table II.3.1.

Table II.3.1 Summary of 13 parameters used for further analysis.

| Parameter | Abbreviation | Unit |
|---|---|---|
| Basal volume | b.v. | ml |
| Basal bicarbonate concentration | b.b.c. | mmol/l |
| Basal chymotrypsin concentration | b.c.c. | U/ml |
| | | |
| Peak volume | p.v. | ml |
| Peak bicarbonate concentration | p.b.c. | mmol/l |
| Peak bicarbonate output | p.b.o. | mmol |
| Peak chymotrypsin concentration | p.c.c. | U/ml |
| Peak chymotrypsin output | p.c.o | U |
| | | |
| Total volume | t.v. | ml |
| Mean bicarbonate concentration | m.b.c. | mmol/l |
| Total bicarbonate output | t.b.o. | mmol |
| Mean chymotrypsin concentration | m.c.c. | U/ml |
| Total chymotrypsin output | t.c.o. | U |

These 13 parameters were calculated as follows:

- Basal values represent results obtained in basal portions.
- Peak volume is the sum of the 2 consecutive highest volumes during stimulation; similarly peak outputs are the sums of the 2 consecutive highest bicarbonate and chymotrypsin outputs respectively.
- Peak concentrationsrepresent the highest bicarbonate or chymotrypsin concentration during stimulation.
- Total volume and outputs are the sum of all values during stimulation.
- Mean concentrations are the mean of all bicarbonate or chymotrypsin concentrations during stimulation.

In order to assess the recovery rate of the test procedure outlined above, studies were done in 6 patients who were, although completely comparable to the other patients in all respects, not included in the analysis of the test results.

Recovery was assessed in the following way: to the Dreiling tube a third lumen of polythene tubing was attached, through which polyethylene glycol (P.E.G.) 4000 was administered in a concentration of 10g/l at a rate of 5 ml/min. The distal opening of this third lumen was located 5 cm. distal to the most distal opening of the gastric portion of the tube. In this way the duodenal lumen is perfused constantly with the marker P.E.G. 4000 and the ratio between the amount of marker recovered from the duodenum and the amount infused is the recovery rate. P.E.G. concentration in duodenal contents were estimated according to the method of Boulter and McMichael (1970). The following formula was used to calculate the recovery rate:

$$\text{Recovery rate} = \frac{\text{Total volume (l)} * \text{P.E.G.concentration (mg/l)}}{\text{amount of P.E.G. infused (mg)}} * 100$$

II.3.1.2 Statistical analysis.

It has been outlined above that the secretin-CCK test produced 13 parameters for each patient. These parameters were used for further analysis and fed into a DEC 20 computer (Digital) together with the following variables of each patient: age; sex; number of diagnostic group (1 to 7); alcohol abuse or not; body weight; E.R.C.P. findings (see chapter II.5); faeces chymotrypsin concentration.

Mean values and standard deviation of each parameter were calculated for each diagnostic group (1 to 7) and for each subgroup, i.e. alcoholic or nonalcoholic. All data were also calculated after division by body weight.

In order to test hypotheses concerning differences of the variables between several groups of patients, the unpaired Student's t-test was used (two-sided). For differences of discrete variables between groups the chi-square test was used, with the Yates' correction where indicated (Swinscow, 1981).

For the interpretation of the secretin-CCK test data the method of discriminant analysis was used (Lachenbruch, 1975). With this method it is possible first to select one or more parameters with optimal discriminating capacity, and second to construct with these parameters a mathematical function that serves to distinguish between two or more groups of patients, the so called allocation rule. This allocation rule incorporates the selected parameters and substitution of the values for an individual will yield a set of results that allocates the individual to one of the groups. In the present study the step by step selection of parameters was determined amongst others by Wilk's criterium and the misclassification rate.

An inevitable drawback of such a retrospective procedure is that the interpretation method (the allocation rule in this case) is applied to the same population in which it was obtained. When this allocation rule is applied to a new group of patients, the classification error will probably be greater. In order to verify our allocation rule, we have used split patient groups in the following manner.

There were two sets, a group of patients with chronic pancreatitis, group CP, and a group of patients without organic disease, group ND. Each of these both groups was randomly split into 2 subgroups: thus, four subgroups were created, 2 with chronic panceatitis, CP and CP*, and two without organic disease, ND and ND*. By combining one subgroup of patients with chronic pancreatitis (CP) with a subgroup of controls (ND), a new subset was obtained for discriminant analysis of the secretin-CCK test data. In that way, a new allocation rule was produced that was subsequently applied, in a prospective way, to the 2 remaining subgroups, CP* and ND*. Finally, this procedure was reversed by performing discriminant analysis on the combined subset CP* and ND* and applying the result to the subgroups CP and ND.

## II.3.2 Results

### II.3.2.1 Presentation of mean and standard error of secretin-CCK test parameters

Values for each diagnostic group

As outlined above, for each patient 13 secretin-CCK test parameters were obtained. Figure II.3.2 shows the mean and standard error for each parameter within each group. The same data are also presented in Appendix A. The secretin-CCK test failed in two patients, one in group 4 and one in group 7. Thus, the results of 297 patients are shown.

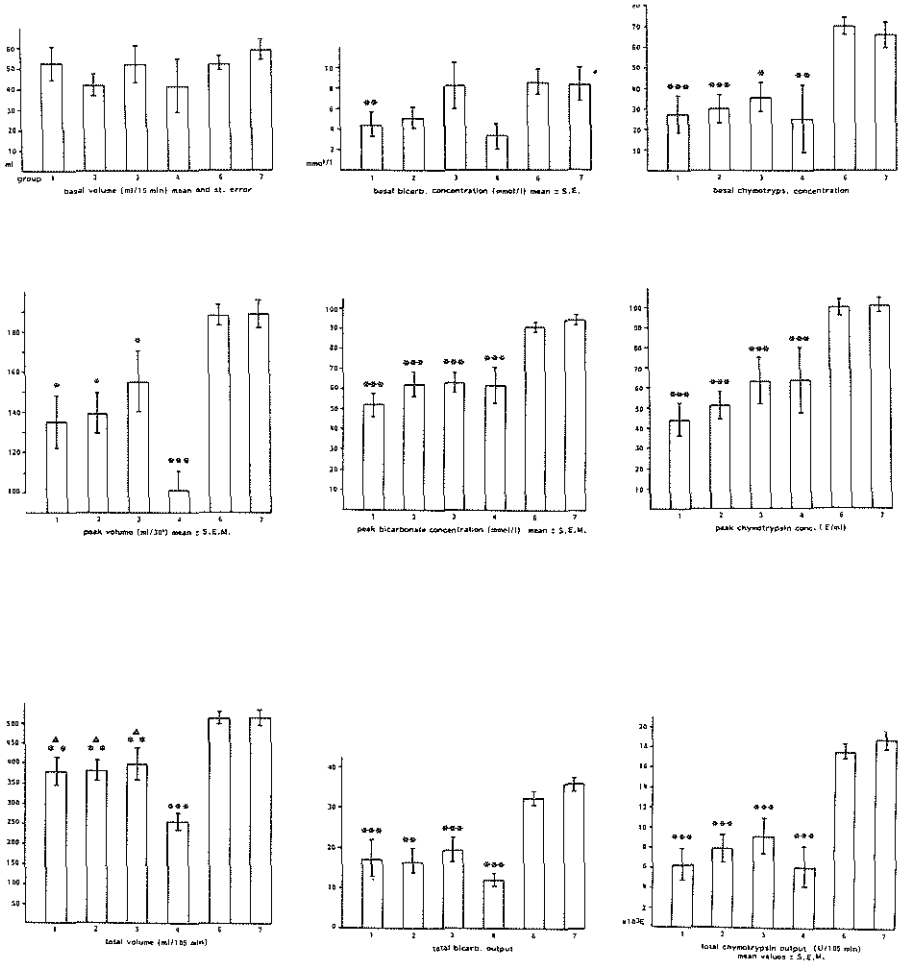
Student's t-tests have been performed on these data as the distribution of the values was not markedly skewed. The results of the Student's t-tests are indicated in the Figure.

The basal volumes for the various groups were not significantly different. The basal bicarbonate concentration in group 1, patients with histologially proven chronic pancreatitis was significantly reduced compared to group 7, the patients without organic disease, but between other groups no statistically significant differences were found. The basal chymotrypsin concentration in groups 1,2 and 3 (chronic pancreatitis and suspected chronic pancreatitis respectively) was significantly reduced compared to group 7. The difference between group 4, patients with pancreatic cancer, and group 7, patients without organic disease, was not statistically significant.

All parameters after stimulation (both peak and total/mean values) in groups 1, 2, 3 and 4 were significantly reduced compared to group 7. Between group 1 (histological proof of chronic pancreatitis) and group 4 (pancreatic cancer) only total volume was significantly different. No statistically significant differences were detected between group 6 (patients with other diagnoses) and and group 7 (patients without organic disease).

Influence of sex on secretin-CCK parameters.

Mean values for each parameter of patients of group 7 (without organic disease) were calculated for men and women separately and are presented in table II.3.2. Significantly lower peak and total volumes were found in women. Bicarbonate concentrations, both peak and mean, did not differ significantly, and the chymotrypsin concentrations were lower in women but the differences were not statistically significant. Consequently, peak and total chymotrypsin output in females were significantly lower than in males.




group 1,2,3,4 vs 7

| | |
|---|---|
| * | 0.01 < p < 0.05 |
| ** | 0.001 < p < 0.01 |
| *** | p < 0.001 |

group 1,2,3 vs 4

| | |
|---|---|
| Δ | 0.01 < p < 0.05 |
| ΔΔ | 0.001 < p < 0.01 |
| ΔΔΔ | p < 0.001 |

Figure II.3.2 Mean and S.E. of S-CCK test parameters in each group. See also Appendix A for details on groups.

Table II.3.2 Sex differences for all 13 parameters in patients without organic disease.

| Parameter | Males n=50 Mean | S.D. | Females n=19 Mean | S.D. | p = |
|---|---|---|---|---|---|
| b.v. | 62.13 | 50.13 | 48.33 | 34.15 | >0.05 |
| b.b.c. | 9.26 | 14.36 | 6.19 | 9.37 | >0.05 |
| b.c.c. | 72.41 | 47.15 | 52.38 | 45.68 | >0.05 |
| p.v. | 197.17 | 60.97 | 168.86 | 32.96 | <0.01 |
| p.b.c. | 93.51 | 19.68 | 98.03 | 21.40 | >0.05 |
| p.b.o. | 15.18 | 5.38 | 13.89 | 4.67 | >0.05 |
| p.c.c. | 105.89 | 36.24 | 88.86 | 23.85 | >0.05 |
| p.c.o. | 18288 | 7034 | 12602 | 4068 | <0.001 |
| t.v. | 549.74 | 167.32 | 439.76 | 106.07 | <0.01 |
| m.b.c. | 67.39 | 18.70 | 71.86 | 24.00 | >0.05 |
| t.b.o. | 37.41 | 14.68 | 32.56 | 14.13 | >0.05 |
| m.c.c. | 84.91 | 25.00 | 74.81 | 22.38 | >0.05 |
| t.c.o. | 21105 | 8097 | 14010 | 5128 | <0.001 |

For interpretation of abbreviations see table II.3.1

Mean and standard error for alcoholic and nonalcoholic subgroups

Figure II.3.3. presents the mean and standard errors of the 13 parameters for each of the alcoholic and nonalcoholic subdivisions of the 7 diagnostic groups.

Differences were looked for between each alcoholic (A) and nonalcoholic (N) subgroup with the Student's t-test. Between subgroups 1A and 1N, between subgroups 2A and 2N and between subgroups 7A and 7N no statistically significant differences were found. Peak and total volume were significantly lower in subgroup 3N compared to subgroup 3A. Group 4 (patients with pancreatic cancer) was too small to allow statistically reliable conclusions on the subgroups. Basal and total volume of subgroup 6N were significantly lower than of subgroup 6A. The differences between the peak volumes of these two subgroups were not statistically significant ($p>0.05$). See figure II.3.3 and appendix B.

Mean values and standard error divided by body weight.

The 13 parameters were divided by the body weight (if available) and these values are presented in appendix C, together with the result of Student's t-tests.

Essentially the same differences between the groups are found as in the plain values (Figure II.3.4 and appendix C), but the standard errors are much higher in the weight corrected

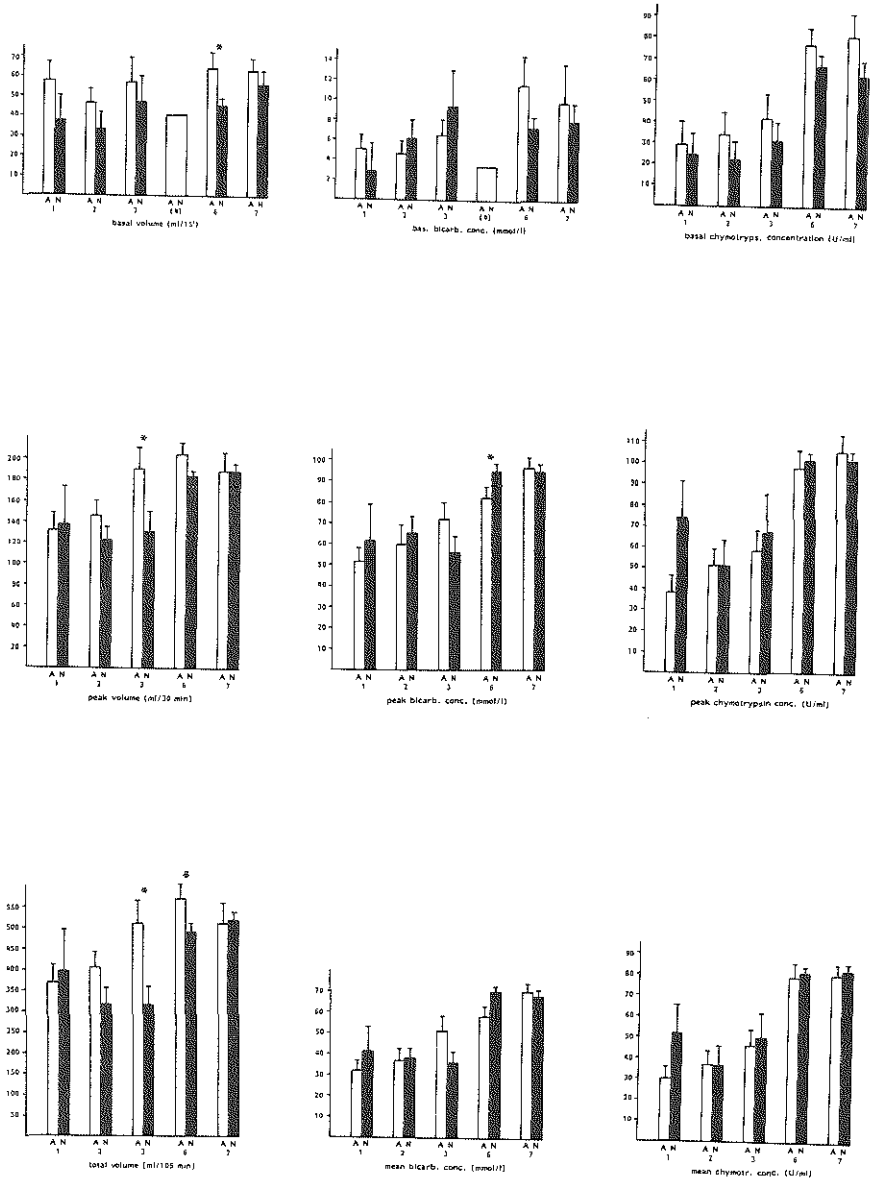


Figure II.3.3 Mean and S.E. of alcoholic and nonalcoholic subgroups. See Appendix B for details. *= $p<0.05$

values compared to the plain values. This makes the weight corrected values less suitable for clinical application.

Mean values and standard error in diabetics.

In chapter I.2.1.2.3 it was noted that impaired exocrine pancreatic function may occur in patients with diabetes mellitus but without chronic pancreatitis. Therefore, we have analysed the secretin-CCK test data of our patients with diabetes who had no evidence of nonacute pancreatic disease, i.e. patients in groups 6 and 7. Table II.3.3 presents the mean and standard errors for peak volume, bicarbonate concentration and chymotrypsin concentration in 14 patients with various degrees of diabetes without pancreatic disease. No statistiscally significant differences between these values and those of patients without diabetes (the remaining patients of groups 6 and 7) were detected.

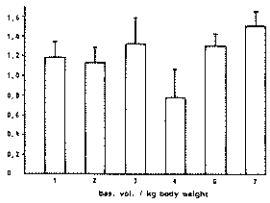
Table II.3.3 Mean and standard error for peak volume and bicarbonate and chymotrypsin concentration in patients with an without diabetes who had no evidence of pancreatic disease.

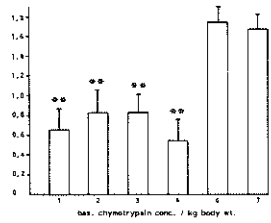
| Patients | | Peak volume | Peak concentration of bicarbonate | chymotrypsin |
|---|---|---|---|---|
| Diabetes | n= 14 | 163 ± 45 ml | 93 ± 21 mmol/l | 92 ± 42 U/ml |
| Group 6 | n=107 | 188 ± 60 | 91 ± 26 | 100 ± 43 |
| Group 7 | n= 67 | 188 ± 55 | 95 ± 20 | 101 ± 34 |

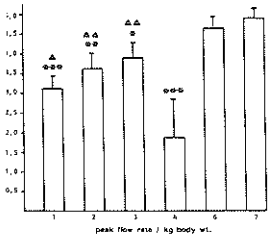
Mean values and standard error after gastric operations.

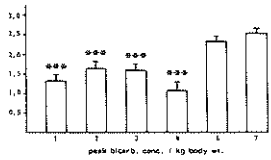
Table II.3.4 presents the mean and standard errors for peak volume, peak bicarbonate and peak chymotrypsin concentrations of patients without pancreatic disease (patients in group 6 & 7) who had had gastric operations in the past: truncal vagotomy, highly selective vagotomy or partial gastrectomy.

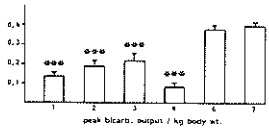
Statistically significant reductions were found for peak volume and peak bicarbonate concentration in patients after gastrectomy compared to the remaining patients in groups 6 & 7. No differences were found between parameters of patients after vagotomy and parameters of the remaining patients without pancreatic disease, particularly volume and bicarbonate concentration were not reduced after truncal or highly slective vagotomy.

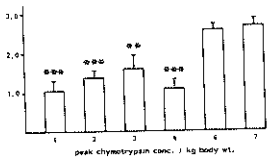


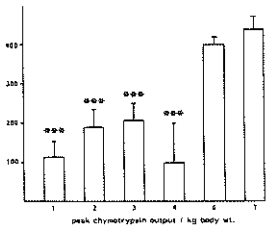




group 1,2,3,4 vs 7

* 0.01 < p < 0.05

** 0.001 < p < 0.01

*** p < 0.001

group 1,2,3 vs 4

Δ 0.01 < p < 0.05

ΔΔ 0.001 < p < 0.01

ΔΔΔ p < 0,001

Figure II.3.4 Mean and S.E. corrected for body weight in each group. See also Appendix C for details.

Table II.3.4 Peak volume, bicarbonate and chymotrypsin concentration (mean and standard error) of 22 patients with and 166 patients without previous gastric surgery, all without pancreatic disease

| Type of operation | p.v. ml | p.b.c.mmol/l | p.c.c. U/ml |
|---|---|---|---|
| HSV & TV n= 6 | 158 ± 29 | 95 ± 13 | 101 ± 16 |
| Gastrectomy n= 16 | 140 ± 39*** | 60 ± 16*** | 103 ± 53 |
| Rest group 6 n=105 | 192 ± 60 | 93 ± 26 | 100 ± 43 |
| Rest group 7 n= 61 | 191 ± 55 | 96 ± 20 | 100 ± 34 |

TV = Truncal vagotomy
HSV = Highly selective vagotomy
Difference compared to group 6/7
*** = $p<0.001$

II.3.2.2 Recovery studies

Recovery rates were calculated in 6 patients, not included in the series, but otherwise comparable in all respects. The following results were obtained (Table II.3.6).

Table II.3.6 Recovery rates in 6 patients

| Patient | Total volume(ml) | Recovery rate(%) |
|---|---|---|
| A | 434 | 88.8 |
| B | 528 | 98.6 |
| C | 295 | 50.6 |
| D | 406 | 116.0 |
| E | 284 | 97.4 |
| F | 360 | 61.7 |
| Mean | | 85.5 |

### II.3.2.3 The application of the secretin-CCK test in clinical practice.

In the section I.3.1.1.1.2 it was explained that problems arise in the interpretation of multiple sets of data, like the results of the secretin-CCK test, and that specific solutions have to be found for these problems. The results of the test presented in section II.3.2.1 are obviously not suitable for the distinction between patients with a normal exocrine pancreatic function and patients in which this function is impaired. Thus, discriminant analysis was applied to these results.

First, all 13 parameters were assessed as to their ability to discriminate between patients with chronic pancreatitis (groups 1 and 2) and patients without organic disease (group 7). A selection of parameters was carried out as follows. Seven parameters were selected by Wilk's criterium. According to the sequence of selection by this step by step method, 7 discriminant analyses were done. Beginning with the first selected parameter, the number of parameters was expanded one by one. The error rate of every combination of parameters was assessed as shown in table II.3.7.

Table II.3.7 Error rates of 7 accumulating combinations of parameters, selected by Wilk's criterium.

| Parameter(s) | Percentage of correct results In group 1+2 | In group 7 | Error rate |
|---|---|---|---|
| M.c.c. | 78 | 84 | 19 |
| + p.b.o. | 82 | 88 | 15 |
| + p.v. | 79 | 91 | 15 |
| + m.b.c. | 75 | 88 | 18 |
| + b.b.c. | 75 | 88 | 18 |
| + p.c.c. | 76 | 90 | 17 |
| + t.c.c. | 76 | 91 | 16 |

For interpretation of abbreviations, see table II.3.1

Selection by Wilk's criterium alone carries the risk of non-optimalisation of the error rate (Habbema & Hermans, 1977).Selection directly based on the error rate was not feasible with the available computer software. Therefore, this intermediate procedure was used. Parameter 'mean chymotrypsin concentration' alone was able to classify 78% of the patients with chronic pancreatitis and 84% of the patients without organic disease correctly. When combined with parameter 'peak bicarbonate output' these figures rose to 82% and 88% with an

overall accuracy, = (100 - error rate), of 85%. Addition of parameters increased the error rate. Therefore, the combination of two parameters (mean chymotrypsin concentration and peak bicarbonate output) was chosen for further analysis.

The next step was to construct an allocation rule in which these two parameters were incorporated. The allocation rule, which yields a Z-score for each secretin-CCK test after substitution of the 2 parameters, was:

$$Z = 0.05 * m.c.c. + 0.14 * p.b.o - 4.36$$

This rule, if Z=0, represents the border between two groups of patients, respectively with chronic pancreatitis and without organic disease: patients with a Z-score below 0 are considered to have an abnormal test and patient with a Z-score above 0 have a normal test result. Figure II.3.7 shows the graphical representation of the patients of groups (1+2) and 7, in a diagram in which the mean chymotrypsin concentration was plotted against the peak bicarbonate output. Thus, each patient was characterised by the values of these two parameters. In this figure is also shown an allocation rule. It will be clear that it is possible to allocate more patients to either one group (i.e. normal or abnormal test result) by shifting the line that represents the allocation rule, thus varying the number of false positive and false negative tests, or of sensitivity and specificity. In order to select the optimal sensitivity and specificity, one may construct a 'receiver operator characteristic' curve in which sensitivity and specificity are plotted against each other (O'Donnell, Pauker et al, 1980). Such an R.O.C. curve of our data is shown in figure II.3.8. On the basis of this 'receiver operator characteristic' curve the allocation rule cited above was considered the yield optimal results: a sensitivity of 82% and a specificity of 88% with an overall accuracy of 85%. Thus, from now on, we can calculate the Z-score of each individual tested by substitution of the data obtained for both parameters in the allocation rule. When $Z<0$, the test is considered abnormal, when $Z>0$, the secretin-CCK test result will be called normal.

The Z-scores of the patients of groups 3,4, 5 and 6 were calculated and the resulting data are presented in table II.3.8, together with the data of groups 1,2 and 7.

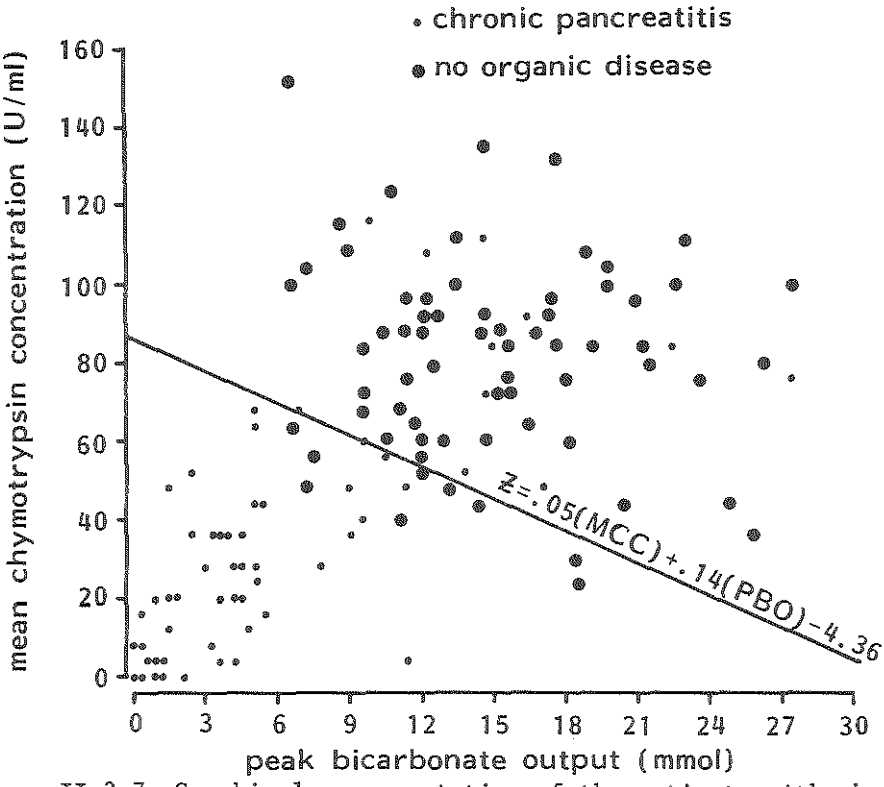
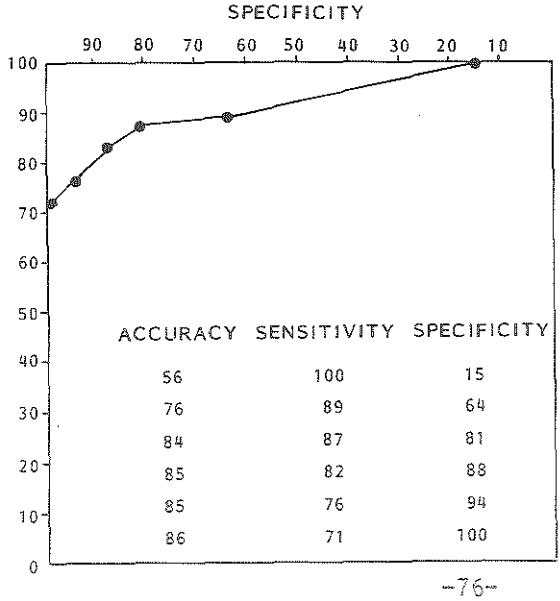



Figure II.3.7 Graphical representation of the patients with chronic pancreatitis and patients without organic disease by their respective values of mean chymotrypsin concentration and peak bicarbonate output. The line represents the allocation rule if Z=0.




| ACCURACY | SENSITIVITY | SPECIFICITY |
|---|---|---|
| 56 | 100 | 15 |
| 76 | 89 | 64 |
| 84 | 87 | 81 |
| 85 | 82 | 88 |
| 85 | 76 | 94 |
| 86 | 71 | 100 |

Figure II.3.8 Receicer operator characteristic curve values for sensitivity and specificity at various positions of the allocation rule.

Table II.3.8 Results of discriminant analysis for each diagnostic group.

| Group | Size | Number classified incorrectly | Correctly classified Number | Percentage |
|---|---|---|---|---|
| 1 | 25 | 3 | 22 | 88 |
| 2 | 38 | 8 | 30 | 79 |
| 3 | 34 | 10 | 24 | 71 |
| 4 | 10 | 3 | 7 | 70 |
| 5 | 2 | 2 | 0 | 100 |
| 6 | 120 | 15 | 105 | 88 |
| 7 | 68 | 8 | 60 | 88 |
| Total | 297 | 47 | 250 | 84 |

In chapter II.3.1.2 attention was drawn to the fact that application of the allocation rule constructed on the basis of these patients to a new population might produce a greater classification error. We have already explained that we can verify our results by repeating the procedure on split patient groups. Thus, the patients with chronic pancreatitis were randomly split into two subgroups CP and CP*, 31 and 32 patients respectively. Similarly, patients without organic disease were randomly divided over two subgroups ND and ND*, 33 and 34 patients respectively. An allocation rule was constructed with parameters: mean chymotrypsin concentration and peak bicarbonate on the basis of the subset CP + ND. This allocation rule, that will not be written down here, was applied to the subset CP* + ND*. See table II.3.9. By the previously described 'retrospective' allocation rule, 16% of the subjects in subgroup CP* had been misclassified. By the 'prospective' allocation rule, 22% of the patients in CP* was incorrectly classified. Of the patients in subgroup ND* 15% had been misclassified by the 'retrospective' allocation rule; now, with the prospective allocation rule obtained in the subset CP + ND 6% was classified wrongly. Similarly, when discriminant analysis was done on the subset CP* + ND* and the resulting allocation rule applied to the subgroups CP and ND, the number of misclassified subjects changed only slightly. Overall, 11 patients with chronic pancreatitis and 8 patients without organic disease were classified incorrectly by the 'retrospective' allocation rule; a 'prospective' allocation rule misclassified 14 patients with chronic pancreatitis and 9 without organic disease. The difference is not clinically significant.

Table II.3.9 Number and percentage of patients classified incorrectly by retrospective and by prospective allocation rules.

| Subgroups | Percentage incorrect classifications | | Number incorrect classifications | |
|---|---|---|---|---|
| | Retro- | Prospective | Retro- | Prospective |
| CP n=31 | 9 | 23 | 11 | 14 |
| CP* n=32 | 16 | 22 | | |
| ND n=33 | 16 | 21 | 8 | 9 |
| ND* n=34 | 15 | 6 | | |
| Total 130 | 15% | 18% | 19 | 23 |

II.3.2.4 Diagnostic performance of the secretin-CCK test in chronic pancreatitis.

In order to assess the diagnostic performance of the secretin-CCK test in chronic pancreatitis, we compared the results of the test in patients with chronic pancreatitis, histologically proven (group 1) and clinically diagnosed (group 2), with the results of patients without nonacute pancreatic disease (groups 6 and 7). Table II.3.10 shows the data.

Out of 63 patients with chronic pancreatitis, 52 had an abnormal test ($Z<0$), which means that the **sensitivity** was 82%.

Out of 188 patients without chronic pancreatitis, pancreatic cancer or cystic fibrosis, 165 had a normal test ($Z>0$), which gives a **specificity** of 88%.

Out of 75 patients with an abnormal test, 52 appeared to have chronic pancreatitis. Thus the **positive predictive value** was 69%.

Out of 176 patients with a normal secretin-CCK test, 165 did not have evidence of pancreatic pathology. Thus, the **negative predictive value** of the test was 94%.

Out of 251 patients with or without chronic pancratitis, 217 were classfied correctly by the test. The **overall accuracy rate** was therefore 86%.

Table II.3.10 Results of the secretin-CCK test in 63 patients with chronic pancreatitis and 188 patients who had no evidence of chronic pancreatic disease.

| | $Z<0$ | $Z>0$ | Total |
|---|---|---|---|
| Chronic pancreatitis (group 1 + 2) | 52 | 11 | 63 |
| No chronic pancreatic disease (group 6 + 7) | 23 | 165 | 188 |
| Total | 75 | 176 | 251 |

### II.3.2.5 The secretin-CCK test in patients with pancreatic cancer.

The discriminant analysis that resulted in the allocation rule presented in section II.3.2.4, was performed in order to separate patients with chronic pancreatitis from patients with similar signs and symptoms but without evidence of chronic pancreatic pathology. Application of this allocation rule to the 10 patients with pancreatic tumors in whom the secretin-CCK test had been performed satisfactorily, classified 7 of them into the group of patients with an abnormal test. An attempt was made to perform discriminant analysis on 3 groups of patients: chronic pancreatitis, pancreatic tumor and controls, but the size of the tumor group was too small in comparison to both other groups (10 versus 63 and 68 respectively) to allow reliable analysis. Thus, the test results of patients with pancreatic tumors were interpreted by an allocation rule destined to identify patients with chronic pancreatitis.

## II.3.3 Evaluation of the secretin-CCK test results

Methodological aspects

The test procedure used was comparable to the schedule described by Wormsley (1969[a,b]). The continuous and simultaneous infusion of secretin and cholecystokinin has several advantages as has been outlined in section I.3.1.1.1.2:

- Maximal stimulation of the hydraletic and ecbolic response (Wormsley, 1969[b]).
- Reproducible results (Petersen, 1969[b]).
- Hardly any side effects because low doses of each hormone are used.

The reason to sample duodenal contents for a period longer than 60 minutes has also been stressed (Gullo, Costa et al, 1976; Gullo, Costa & Labo, 1978).

During the period of observation, natural GIH cholecystokinin was replaced by the synthetic octapeptide sincalide in a dose equivalent to the previously used dose of 1 IDU/kg/hour GIH cholecystokinin, namely 40 ng/kg/hour (Ondetti, Rubin et al, 1970; Dockray, 1973; Thulin, 1973). The simultaneous infusion of secretin GIH 0.25 CU/kg/hour and sincalide 40 ng/kg/hour has been reported to induce maximal stimulation of the enzyme output in man (Regan, Go et al, 1978).

The performance of the secretin-CCK test in our series very seldom caused any problems. Introduction of the double lumen tube was almost always accomplished without much discomfort to the patient. Only two tests out of 299 were

considered to have failed because of technical problems. All tests were done by nursing staff,usually two patients in one morning session.

Recovery rates were assessed in 6 patients in order to be allowed to draw conclusions from the parameters that are dependent on the volume of the duodenal contents. As the recovery rates in this small group of patients was rather high and fully comparable to those reported by others, it appears to be permissible to use the volume dependent parameters for further detailed analysis (Lagerlöf, Schütz & Holmer, 1967; Schütz, Anderson & Lagerlöf, 1969; Tympner, Domschke et al, 1974[b]).

Mean values and standard errors in various groups

Analysis of the mean values for each parameter obtained in each diagnostic group (1 to 7) and in the alcoholic and non-alcoholic subgroups, yielded no unexpected results.

Basal bicarbonate and chymotrypsin concentrations were lower in patients with chronic pancreatitis compared to patients without organic disease. There was no significant increase in basal chymotrypsin concentrations of alcoholics versus non-alcoholics. Such an increase might be expected on the basis of the theory that increased protein concentrations are of pathogenetic importance in alcoholic pancreatitis (Sarles & Sahel, 1976).

After stimulation with exogenous hormones the mean values of all parameters of patients with chronic pancreatitis (proven and suspected) and pancreatic tumors were significantly reduced compared to the values of patients known not to have chronic pancreatic disease. The total volume in patients with pancreatic tumors was significantly lower than in patients with chronic pancreatitis. The finding that there were no significant differences between mean values of the parameters of patients in group 6 and 7 indicated that these parameters are correlated specifically to pancreatic pathology and not to the general condition of the patient, although impairment of exocrine pancreatic function in malnutrition has been reported.

Statistically significant differences between alcoholic and nonalcoholic subgroups were seen only sporadically and are not readily explained other than by chance fluctuation. It has to be noted that out of 78 differences compared, only 6 (i.e. 8%) were significant at the level $p < 0.05$. In patients with suspected chronic pancreatitis, peak and total volume were reduced in the nonalcoholic subgroup compared to the values in alcoholics (group 3A) and in controls (groups 7A and 7N). On the other hand, total volume in alcoholic patients with other diagnoses (group 6A) was significantly higher than in nonalcoholic patients (6N) and in patients without organic disease (group 7). Between alcoholics and nonalcoholics with chronic pancreatitis

no statistically significant differences could be demonstrated. This might indicate that alcohol abuse leads to an increased volume response in patients without chronic pancreatitis but this effect was not seen in the group of patients without organic disease (group 7). Reduction of volume response occurred in patients with proven chronic pancreatitis and in nonalcoholic patients with suspected chronic pancreatitis. No reduction of volume response was seen in alcoholic patients with suspected chronic pancreatitis. All in all, little support is found in our patients that alcohol abuse leads to pancreatic hypersecretion of water and electrolytes (Dreiling & Wolfson, 1979; Neves, Borges & Vilela, 1983).

In contrast to other series, no advantage resulted from calculating the values per kg body weight (Dreiling & Janowitz, 1962). Instead of a reduction, we found an increase in variance when compared to the plain values.

## Discriminant analysis in the interpretation of the test results

Discriminant analysis has been applied only sporadically to exocrine pancreatic function tests (Capitaine, Cros et al, 1971; Thurmayr, Thurmayr & Otte, 1975). Although the initial performance requires sophisticated computer facilities, the theoretical and practical advantages make it worthwile.

First, the problem of reference values is solved.

Second, discriminant analysis selects the parameters with the highest discriminatory ability and finally it constructs an allocation rule in which these parameters are incorporated. Simple substitution of the values obtained in a patient into the allocation rule provides a reliable test result.

In this series it appeared possible to construct a highly satisfactory allocation rule with only two parameters, namely mean chymotrypsin concentration and peak bicarbonate output, thus simplifying the interpretation of the secretin-CCK test enormously. It was also made likely that application of this allocation rule to new populations will probably not lead to a significantly lower diagnostic performance.

## Results of the secretin-CCK test in the patient groups.

### Group 1

In this group of patients with histologically confirmed chronic pancreatitis, 3 out of 25 had a normal secretin-CCK test. Two of them were alcoholics, one had diabetes and none had calcifications on the plain X-ray. Histological examination, the details of which will be reported in chapter II.6., demonstrated mild changes in all 3. E.R.C.P. failed in 2 of these 3 patients; in 1 patient an inflammatory tumor with a pseudocyst was shown.

Group 2

In the group of patients in whom chronic pancreatitis was diagnosed by clinical and radiological findings, 8 out of 38 had a normal test. Six of them were alcoholics and 2 had diabetes. E.R.C.P. demonstrated changes compatible with chronic pancreatitis in 7 of these 8 patients; in the remaining patient, calcifications had been reported on the plain X-ray but the E.R.C.P. did not show changes of chronic pancreatitis. One other patient with a normal secretin-CCK test result had calcifications of the pancreas.

Table II.3.11 Correlation between the severity of chronic pancreatitis, expressed as the number of signs of advanced disease, and the Z-score of the secretin-CCK test.

| Z-score | Number 0 | 1 | 2 | 3 | Total |
|---|---|---|---|---|---|
| < -2.0 | - | 5 | 7 | 2 | 14 |
| -1.5 -2.0 | 1 | 6 | 3 | - | 10 |
| -1.0 -1.5 | 8 | 2 | 4 | - | 14 |
| -0.5 -1.0 | 3 | - | 2 | - | 5 |
| 0 -0.5 | 8 | - | - | - | 8 |
| > 0 | 7 | 4 | - | - | 11 |
| Total | 27 | 17 | 16 | 2 | 62 |

The severity of chronic pancreatitis can be assessed by the presence of signs of advanced disease, exocrine insufficiency (steatorrhoea), endocrine insufficiency (diabetes) or calcifications on the plain abdominal X-ray. In table II.3.11 the Z-score of the secretin-CCK test has been plotted against the number of factors of severe chronic pancreatitis present in 62 patients (in one patient the records did not provide all details on the severity of chronic pancreatitis). It can be seen that out of 11 patients with chronic pancreatitis who had a normal secretin-CCK test, 7 had no factors of advanced disease and none had more than 1 factor. Out of 27 patients with mild to moderate impairment of the secretin-CCK test ($-1.5<Z<0$), 19 had no factors, 2 had 1 factor and 6 had 2 factors of advanced chronic pancreatitis. Out of 24 patients with severely impaired secretin-CCK tests ($Z<-1.5$), only 1 had no factors and 12 had 2 or more factors of advanced disease. Both patients with 3 factors had a very low Z-score ($<-2.0$).

Group 3

Ten out of 34 patients with suspected chronic pancreatitis had a normal test. Among these 10 were 4 alcoholics. E.R.C.P. was attempted in 6 of them, but failed in 3; in the other 3 patients it showed: a space occupying lesion, signs of acute pancreatitis and no abnormalities respectively. Abnormal ultrasonography findings were recorded in the 3 patients in whom no E.R.C.P. was obtained. These 10 patients did not differ from the remaining 24 patients regarding sex distribution, age and other characteristics recorded in the patients' notes.

It should be stressed that the label 'suspected chronic pancreatitis' was stuck to this group of patients because the investigations did not produce sufficient or consistent results to either accept or eliminate the diagnosis chronic pancreatitis. Therefore, the evaluation of these patients regarding the results of the secretin-CCK test is less valid than that of the other groups, in which diagnoses could be made or eliminated with confidence (groups 1, 2, 4, 5, 6 and 7). Nevertheless, this group of patients with suspected chronic pancreatitis may very well contain a number of subjects with early disease and a follow up of these patients in future might reveal interesting results.

Group 4

The secretin-CCK test failed in 1 out of 11 patients with pancreatic cancer because only minimal amounts of (acid) duodenal contents could be collected. E.R.C.P. in this patient was not possible because of an malformed papilla, probably due to tumor invasion, as laparotomy revealed a large tumor of the head of the pancreas and liver metastases.

Of the other 10 patients 3 had a normal secretin-CCK test result with a Z-score above 0. Two of these 3 had a tumor of the body and 1 had a tumor of the head of the gland.

The small number of patients with a tumor of the pancreas did not allow separate discriminant analysis for this group. It is obvious that discriminant anlysis will have to be done in future after collecting the results of more patients with pancreatic cancer.

Group 5

As expected, both patients with cystic fibrosis and clinical signs and symptoms of exocrine pancreatic insufficiency had an abnormal test.

Group 6

In this group of 120 patients with other diseases than chronic pancreatitis or pancreatic cancer, 15 (12%) had an abnormal secretin-CCK test results. In this section these 15 patients will be analysed in more detail.

In 1 patient, who had had a Roux-en-Y reconstruction after a partial gastrectomy, an anatomical explanation seems likely for the abnormal test result. In 3 female patients a poor general condition with recent weight loss, metabolic derangements and dehydration was present due to Crohn's disease with a short bowel syndrome, primary biliary cirrhosis and abdominal angina in one patient each. One of these patients died 2 weeks after the secretin-CCK test.

In 4 patients the test was performed within six weeks after an attack of acute pancreatitis. Overall, 15 patients with previous attacks of acute pancreatitis had been tested, 6 within a period of six weeks after the last attack. Four of these 6 had an abnormal test results, but no abnormal test results were recorded in 9 patients who were tested more than six weeks after the last attack. The relative proportion of patients with acute pancreatitis and an abnormal test (4/15) is not significantly different from the proportion of patients with other diagnosis and an abnormal test (11/106).

Thus an explanation for the abnormal test results in this group could be identified in 8/15 patients.

Group 7

In this group of 69 patients without a diagnosis, the secretin-CCK test failed in one instance. Eight patients had an abnormal test result. One of them had had a partial gastrectomy with a Billroth II gastrojejunostomy, another patient was found on endoscopy to have a severely scarred duodenal bulb. It is possible that anatomical factors have interfered with the sampling of duodenal contents in these two patients. In the other 6 patients no readily available explanation for the abnormal test results could be found.

The findings in the patients of group 6 and 7 indicate that a time lapse of 6 weeks is advisable after an attack of acute pancreatitis before the secretin-CCK test is performed (Mitchell, Playforth et al, 1983). There were 3 patients with an abnormal test result who were in a poor general condition with recent weight loss and intestinal problems. It seems very well possible that that may explain the results as none of these patients was shown to have pancreatic disease (Gyr, Wolf et al, 1975). **Thus, we conclude that the secretin-CCK test should be interpreted with caution in patients with a poor general condition, in patients with a grossly altered anatomy of the upper gastrointestinal tract and in patients who have had an attack of acute pancreatitis less than 6 weeks ago.**

Patients after gastric surgery.

In the previous section it was mentioned that two patients (1 in group 6 and 1 in group 7) without chronic pancreatic disease had an abnormal secretin-CCK test after previous partial gastrectomy. Besides the anatomical changes in these patients (Roux-en-Y and Billroth II reconstruction respectively) that might have interfered with the sampling of duodenal contents, the possibility that other factors have played a role should be investigated (see section I.1.2.2.1). In this section we will therefore analyse the secretin-CCK test results of patients without chronic pancreatic disease who had had some form of gastric surgery in the past. Table II.3.12 presents the test results of 22 patients of group 6 and 7 after various types of gastric operations.

Out of 22 patients with previous gastric operations and a succesful secretin-CCK test , the result was abnormal in 2. The figure is not significantly different form the proportion of patients in group 6 and 7 who had had no gastric operations, 21/166 (13%).

In section II.3.2.1 we have reported the finding that the 16 patients without chronic pancreatic disease who had had partial gastrectomies, had on the average a reduction of the peak volume and bicarbonate concentration after stimulation in comparison to the patients in group 6 and 7 who had not had gastric

Table II.3.12 Secretin-CCK test results of patients without chronic pancreatic disease (group 6 and 7) who had had some type of gastric operation.

| Type of operation | Size of group | Number abnormal test results |
|---|---|---|
| Truncal vagotomy | 1 | 0 |
| Truncal vagotomy+antrectomy | 1 | 0 |
| Highly selective vagotomy | 4 | 0 |
| Billroth I | 3 | 0 |
| Billroth II | 11 | 1 |
| Roux-en-Y | 1 | 1 |
| Billroth II & Henley loop | 1 | 0 |
| Total | 22 | 2 = 9% |

operations. It appears that this reduction of the hydraletic response after partial gastrectomy, that has also been reported by others (Wormsley, 1972[b]; see also section I.1.2.2), does not impair the secretin-CCK test result in the majority of patients. **Thus, gastric surgery per se, without gross changes in anatomy, does not lead to abnormal secretin-CCK test results.**

Patients with diabetes mellitus

In table II.3.13 the results of secretin-CCK tests of patients with diabetes with and without pancreatic disease are presented. Overall, 41 patients with diabetes were tested. Half of them, 21, had chronic pancreatitis (group 1 and 2) and in 18 of these or 86% an abnormal test result was obtained. All diabetic patients in group 3 (suspected chronic pancreatitis) and group 4 (pancreatic cancer) had an abnormal test.

Of the 14 diabetics without chronic pancreatic disease, 3 had an abnormal test (21%); of the 174 remaining patients in groups 6 and 7, 20 had an abnormal test. The frequency of abnormal secretin-CCK test results in diabetics is not significantly different from that in nondiabetic patients without pancreatic pathology. The number of diabetics in groups 6 and 7 was too small for classification into subgroups according to the severity of diabetes, but it is interesting to note that 1 out of 2 insulin requiring diabetics and 1 out of 3 patients regulated with oral hypoglycaemics had an abnormal test result compared to 1 out of 9 patients with diet regulated or latent diabetes.

Impairment of exocrine pancreatic function in diabetics has been the subject of several reports (Chey, Shay & Shuman, 1963; Baron & Navarro, 1973; Frier, Saunders et al, 1976). It has been proposed intimate relationships exist between the endocrine and

Table II.3.13 Results of secretin-CCK tests in patients with and without diabetes mellitus.

| Group | Size of diabetic group | | Patients with abnormal test | |
|---|---|---|---|---|
| | Number | % | Number | % |
| 1+2 | 21 | 33 | 18 | 86 |
| 3 | 4 | 12 | 4 | 100 |
| 4 | 2 | 20 | 2 | 100 |
| 6+7 | 14 | 7 | 3 | 21 |

the exocrine pancreas. In our series, half of the patients with diabetes had confirmed chronic pancreatitis, 4 had suspected chronic pancreatitis and 2 had a tumor of the pancreas. The frequency of abnormal test results in patients without pancreatic disease was not significantly higher in patients with diabetes than in patients without diabetes. Impairment of exocrine pancreatic function appeared to occur more frequently in patients with insulin or drug dependent diabetes than in patients with diet regulated or latent diabetes.

In summary, out of 23 patients without chronic pancreatic disease who had an abnormal secretin-CCK test result, a possible explanation for this finding could be detected in 8: recent acute pancreatitis in 4, poor general condition in 3 and grossly changed anatomy in 1 patient. When these 8 patients, in whom the test should probably not have been performed in retrospect, are excluded from the series, the specificity of the test increases from 88 to 92% and the positive predictive value rises from 69 to 78%, with an overall accuracy of 89% (see table II.3.14).

Table II.3.14 Results of secretin-CCK test in 243 patients with and without chronic pancreatitis, after exclusion of 8 patients with obvious reasons for abnormal test results. Between brackets the original numbers, see table II.3.10

| | Z<0 | Z>0 | Total |
|---|---|---|---|
| Group 1+2 | 52 | 11 | 63 |
| 6+7 | 15 | 165 | 180 |
| Total | 67 | 176 | 243 |

Specificity: 165/180 = 92%
Positive predictive value: 52/ 67 = 78%
Accuracy: 217/243 = 89%

## II.4 THE SECRETIN-CCK TEST AND CHYMOTRYPSIN CONCENTRATION OF THE FAECES

### II.4.1 Methods

The concentration of chymotrypsin in the faeces was estimated using n-acetyl-tyrosin-ethyl-ester (ATEE) as substrate (Ammann, 1967). Random specimens of faeces were used for this estimation without a special diet or preparation. Care was taken to freeze specimens as freshly as possible, until analysed. Fecal chymotrypsin estimations had not been performed in all patients who came to the secretin-CCK test. In some patients more than one estimation was performed; in these cases the mean value of the results was calculated and used for analysis.

### II.4.2 Results

The mean and standard error of the faecal chymotrypsin concentrations for each diagnostic group (1 to 7, see chapter II.2) and for each subgroup (Alcoholic and Nonalcoholic) are shown in figure II.4.1, together with the results of Student's t-tests to indicate the level of significance between the subgroups. The results are also presented in appendix D.

Only the difference between the mean values of group 2 and group 7 was statistically significant. Between the alcoholic and nonalcoholic subgroups interesting differences were noted: the concentrations of patients in group 1A, 2A and 3A were all significantly lower than the concentrations of patients in subgroups 6A and 7A; the concentration of faecal chymotrypsin in group 7N was significantly lower than that of group 7A.

In this hospital the lower limit of the reference value of faecal chymotrypsin is 30 U/g. faeces. Table II.4.1 presents the fequency of values in our series below this level for each diagnostic group (1 to 7). Of the patients with chronic pancreatitis (groups 1 and 2) 51% had a reduced concentration of chymotrypsin in the faeces. Of the patients without chronic pancreatic disease (groups 6 and 7) 14% had a reduced concentration. In table II.4.1 is also presented the diagnostic performance for chronic pancreatitis of this estimation.

Table II.4.2 and II.4.3 present the correlations between the faecal chymotrypsin concentration and the results of the secretin-CCK test, expressed by the Z-score of the allocation rule, see chapter II.3.

All 29 patients with chronic pancreatitis who had a reduced concentration (<30 U/g) of faecal chymotrypsin, had an abnormal secretin-CCK test, and all 10 patients with chronic pancreatitis who had a normal secretin-CCK test, had faecal chymotrypsin concentrations of 30 U/g or more.

Table II.4.1 Frequency of reduced chymotrypsin concentration in the faeces in each diagnostic group.

| Group | Size of patient group*) | Size of group with reduced concentrations | |
|---|---|---|---|
| | | Number | Percentage |
| 1 | 22 | 12 | 54 |
| 2 | 35 | 17 | 49 |
| 3 | 24 | 9 | 38 |
| 4 | 6 | 2 | 33 |
| 5 | 2 | 2 | 100 |
| 6 | 95 | 9 | 10 |
| 7 | 57 | 13 | 23 |

| | |
|---|---|
| Sensitivity | 29/ 57 = 51% |
| Specificity | 130/152 = 86% |
| Accuracy | 159/209 = 76% |
| Positive predictive value | 29/ 51 = 57% |
| Negative predictive value | 130/158 = 82% |

*) Number of patients in each group of whom faecal chymotrypsin concentration was estimated.

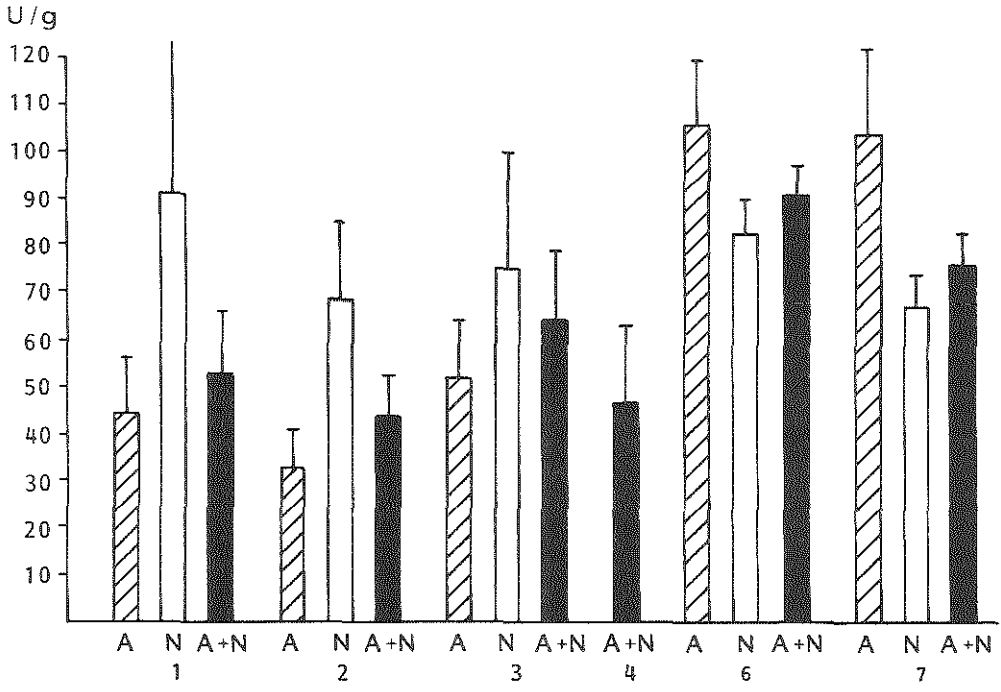



Figure II.4.1 Mean and S.E. of faecal chymotrypsin concentrations in each subgroup. See also Appendix D.

The faecal chymotrypsin concentration of 22 patients without chronic pancreatic disease (group 6 and 7) was reduced. In 4 of these patients the secretin-CCK test was abnormal as well.

Pearson correlation coefficients between faecal chymotrypsin concentration and peak chymotrypsin output and total chymotrypsin output in duodenal contents of all patients were 0.24 each.

Table II.4.2 Correlation between faecal chymotrypsin concentration and results of secretin-CCK test in 57 patients with chronic pancreatitis

| | Number of patients with faecal chymotrypsin concentration | | |
|---|---|---|---|
| Z-score S-CCK test | <30 U/g | >30 u/g | Total |
| Z<0 | 29 | 18 | 47 |
| Z>0 | 0 | 10 | 10 |
| Total | 29 | 28 | 57 |

Table II.4.3 Correlation between faecal chymotrypsin concentration and results of secretin-CCK test in 152 patients without chronic pancreatic disease.

| | Number of patients with faecal chymotrypsin concentration | | |
|---|---|---|---|
| Z-score S-CCK test | <30 U/g | >30 U/g | Total |
| Z<0 | 4 | 12 | 16 |
| Z>0 | 18 | 118 | 136 |
| Total | 22 | 130 | 152 |

Sixteen out of 22 patients with chronic pancreatitis who had calcifications on the X-ray had a reduced faecal chymotrypsin concentration (73%). Of the patients with chronic pancreatitis without calcifications, 13 had a reduced concentration (37%) The difference in frequencies between these two populations is statistically significant ($p<0.05$).

### II.4.3 Evaluation of the results

The method of sampling of faeces for chymotrypsin content was discussed in section I.3.1.2.2.2, where it was explained that collection of 24 hour specimens did not yield better results than random specimens according to the literature.

Overall, the distribution of faecal chymotrypsin concentrations in our patients showed a fairly wide distribution. Significant reductions of concentrations were found in alcoholic patients with chronic pancreatitis compared to alcoholic patients without this disease. In alcoholic patients without organic disease there was a statistically significant higher concentration of faecal chymotrypsin than in nonalcoholics. These findings may be explained by a shortened intestinal transit time in alcoholics (Van Thiel, Lipsitz et al, 1981; Van De Merwe & Mol, 1982).

The diagnostic performance of the faecal chymotrypsin estimation for chronic pancreatitis is rather low. The positive predictive value of 57% is too small for practical purposes, while the negative predictive value of 82% does not justify its use as a screening test.

There was only a weak correlation between faecal chymotrypsin concentration and duodenal chymotrypsin output after secretin and cholecystokinin stimulation. A good correlation was found between the faecal chymotrypsin content and the results of the secretin-CCK test only in patients with chronic pancreatitis but not in patients without pancreatic disease.

Reduced faecal chymotrypsin concentrations occurred significantly more often in patients with calcifications of the pancreas than in patients with chronic pancreatitis without calcifications.

Thus, there appears to be no role for the estimations of faecal chymotrypsin concentration in the diagnosis of nonacute pancreatic disease, e.g. chronic pancreatitis.

## II.5 THE SECRETIN-CCK TEST AND ENDOSCOPIC RETROGRADE CHOLANGIOPANCREATOGRAPHY (E.R.C.P)

### II.5.1 Methods

#### II.5.1.1 E.R.C.P. procedure

In Dijkzigt University Hospital E.R.C.P. is performed by a team of endoscopists and radiologists using a sideviewing endoscope (Fujinon, Olympus) and a teflon cannula with an outer diameter of 1.7 mm. As contrast medium iothalamate is used to which gentamicin is added (80 mg/60 ml). The contrast medium is injected under fluoroscopic control and attempts are made to visualise both the common bile duct and the pancreatic duct in all examinations. Systemic antibiotic prophylaxis is given before and after the procedure (Nix, 1981).

#### II.5.1.2 Interpretation of E.R.C.P films

Because in our departments the indications for E.R.C.P. are strictly adhered to (see section I.3.3.3) films of only a limited number of patients were available. For the purpose of this study, films of 75 patients who had had a secretin-CCK test were reviewed by a single radiologist and the author, using a specially designed protocol. This protocol (presented in table II.5.1) was devised according to the criteria of Kasugai (Kasugai, Kuno et al, 1972; see also section I.3.3.3) with special attention to ductular changes. Our protocol differs from Kasugai's design in the method of recording: instead of a semi-quantitative scale we used a binary scale, which means that each question had to be answered by 'yes' or 'no'.

Subsequently, E.R.C.P. films which showed changes compatible with chronic pancreatitis, were graded in the following way:

I = changes in side branches only
II = changes of the main pancreatic duct
III = presence of complications, like concrements, fistula, pseudocyst or other space occupying lesion

#### II.5.1.3 Statistics

For assessing the association between items of E.R.C.P. films the chi-square test was used. Correlations between parameters of the secretin-CCK test and items of E.R.C.P. were calculated. The results of the secretin-CCK test are compared with the results of E.R.C.P. using McNemar's test.

Table II.5.1 Definition of criteria used in the protocol for reviewing E.R.C.P. films. See also figures II.5.1-4.

Main pancreatic duct

| | |
|---|---|
| Diameter | = Estimation of width of lumen |
| Vagueness of contour | = Delineation of duct not sharp |
| Caliber irregularities | = Multiple stenoses and dilatations of varying degree |
| Tortuosity | = Pathological deviation in the course of the duct |
| Concrements | = Any concrete substance in the lumen, whether or not opaque |

Side branches or ductuli

| | |
|---|---|
| Diameter | = see above |
| Vagueness of contour | = see above |
| Caliber irregularities | = see above |
| Tortuosity | = see above |
| Concrements | = see above |
| Opacity of parenchyma | = Any extravasation of contrast medium outside lumen |
| Inflammatory tumor | = Compressing mass, in which the ductuli are not visible |
| Pseudocyst | = Any cystic lesion in or outside the gland, communicating with the ductal system |
| Malignancy | = Smooth tapered stenosis of duct passable with contrast |
| Ductal stenosis | = Stenosis without malignant characteristics |
| Widened duodenal loop | = Increase in vertical and/or horizontal diameter of the loop |
| Mucosal changes | = Any mucosal changes at the medial or superior border of the duodenum, e.g. spiculations |

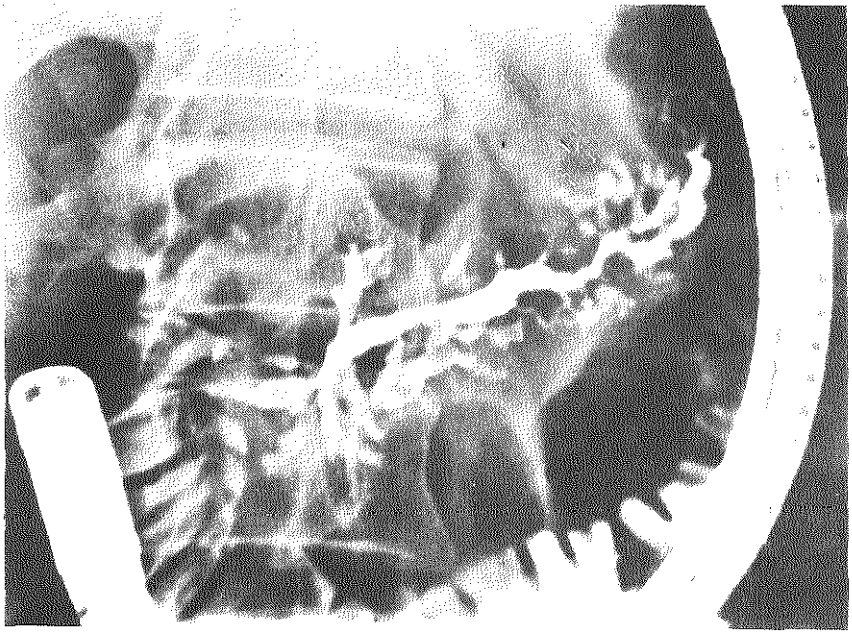


Figure II.5.1 E.R.C.P. in chronic parenchymatous or calcifying pancreatitis. Note intraductal concrements.

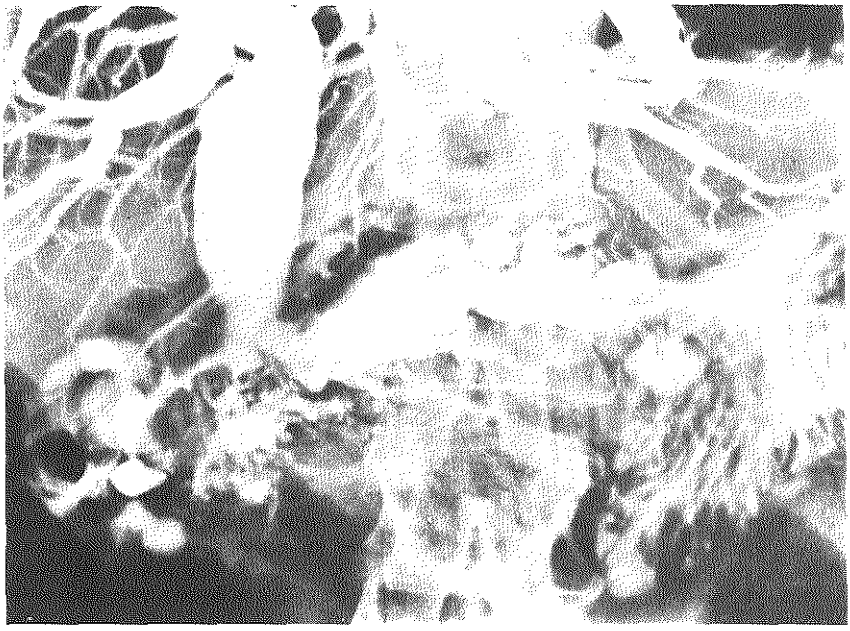


Figure II.5.2 E.R.C.P. in chronic parenchymatous pancreatitis with an inflammatory tumor of the head.

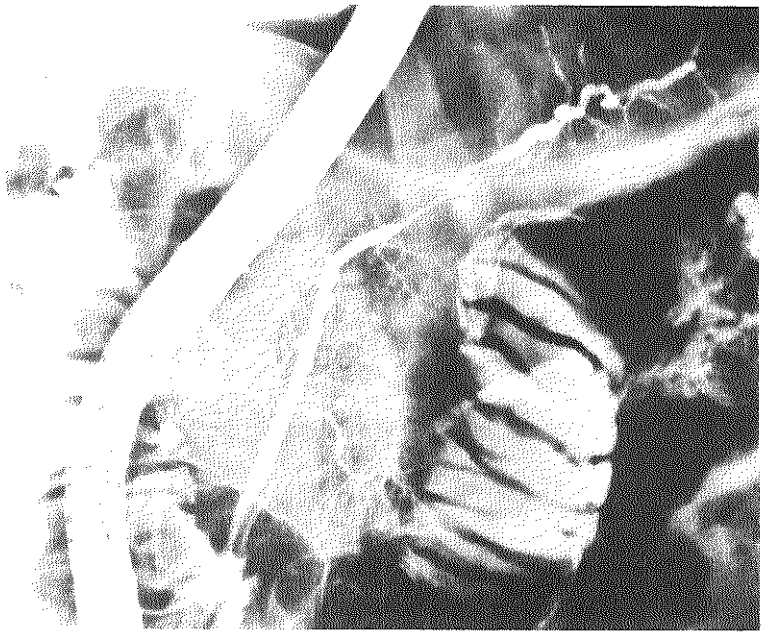


Figure II.5.3 E.R.C.P. with stenosis of the main duct

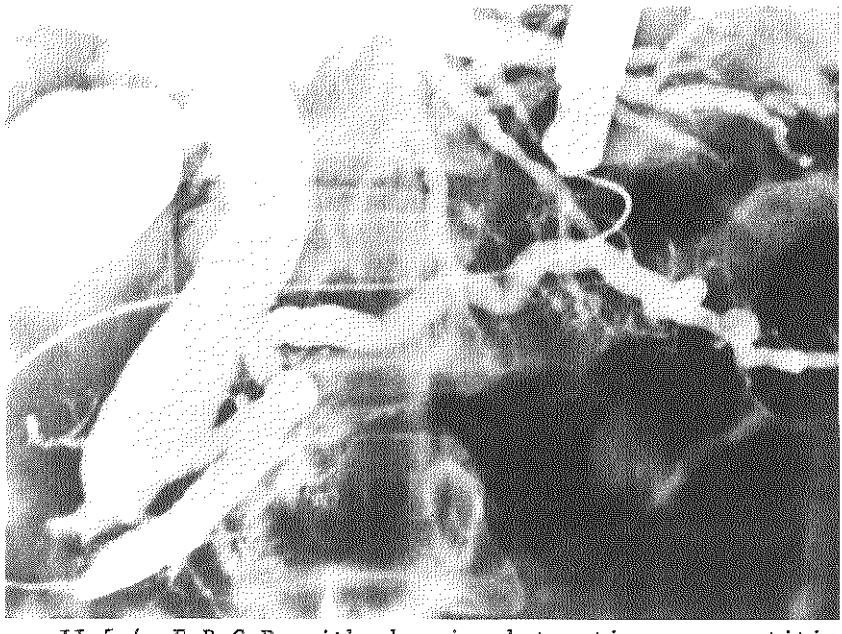


Figure II.5.4 E.R.C.P. with chronic obstructive pancreatitis due to a tumor of the papilla

## II.5.2 Results

### II.5.2.1 Associations between E.R.C.P. items

The absence or presence of E.R.C.P. items, as listed in table II.5.1, were recorded and associations were assessed for the three parts of the pancreas separately. The results of chi-square tests are presented in table II.5.2.

In general, the associations reach higher levels in the tail of the the pancreas; ductular itmes reach higher levels than ductal parameters. All associations are rather high, except those between diameter of the duct and contour vagueness in the head. The items contour vagueness, caliber irregularities and tortuosities are closely related, both at ductal and at ductular level.

### II.5.2.2 Frequency of abnormalities in each group.

Table II.5.3 presents the percentages of abnormalities for each E.R.C.P. item in each diagnostic group (1 to 7, see chapter II.2), for head, body and tail of the pancreas.

These data identify certain parameters as 'hard signs' of chronic pancreatitis, which means that they occur virtually only in patients with the disease, but not necessarily in all patients with chronic pancreatitis. For instance, concrements in duct or ductuli; space occupying lesions; ductular caliber irregularities and tortuosities.

Evaluation of the individual frequencies demonstrated several interesting aspects:

Dilatation of the main duct was seen most frequently in patients with chronic pancreatitis but also in patients with nonpancreatic disease. Although the diameters were estimated and not measured, it appears that this sign (i.e. increased diameter of the duct) is not a very specific one of pancreatic pathology. Vagueness of contour, caliber irregularities and tortuosities of the main duct occurred most often in patients with histologically confirmed chronic pancreatitis (group 1) followed by group 2 and 3, while they were virtually absent in patients of group 6 and 7. Ductal concrements were seen particularly in patients of group 1, mainly in the body of the pancreas.

Increased diameter of the side branches was seen in patients of both group 1 and 2, in a frequency slightly higher than that of ductal dilatation. But an increase in diameter of the ductuli was also seen in more than 15% of the patients in whom no chronic pancreatic disease was found (group 6 and 7). Caliber irregularities and tortuosities, occurring almost as often in group 1 as in group 2, were not recorded in patients in group 6 and 7. Again, concrements in the side branches occurred mainly in patients in group 1, and with a somewhat higher frequency than ductal concrements.

Table II.5.2 Associations of E.R.C.P.items for all 75 patients

| Items | Head chi square | Body chi square | Tail chi square |
|---|---|---|---|
| Main duct | | | |
| Diam-contour | 2.70 | 5.39 | 5.46 |
| Diam-caliber | 12.14. | 23.39 | 17.63 |
| Diam-tortuos. | 8.72 | 11.24 | 19.08 |
| Cont-caliber | 19.01 | 16.40 | 28.66 |
| Cont-tortuos. | 10.67 | 16.14 | 17.18 |
| Calib-tortuos. | 28.92 | 35.12 | 42.71 |
| Ductuli | | | |
| Diam-contour | 13.74 | 24.30 | 19.82 |
| Diam-caliber | 21.44 | 26.09 | 21.13 |
| Diam-tortuos. | 22.49 | 26.60 | 21.08 |
| Cont-caliber | 20.12 | 30.24 | 31.17 |
| Cont-tortuos. | 14.15 | 25.45 | 26.31 |
| Calib-tortuos. | 27.02 | 38.84 | 39.77 |
| Duct versus ductuli | | | |
| Diam-diameter | 10.02 | 24.06 | 29.62 |
| Cont-contour | 10.94 | 15.33 | 22.02 |
| Concrement-concrement | 6.63 | 19.19 | 14.49 |

Legend: Diam = diameter (see also talbe II.5.1)
Cont(our) = vagueness of contour
Calib(er) = caliber irregularities
Tortuos. = tortuosity

Three types of space occupying lesions were recorded:
- inflammatory tumor
- pseudocyst
- malignancy (for definitions, see table II.5.1)

An inflammatory tumor was seen in 12 patients in group 1 and 2, evenly distributed over the parts of the gland. A pseudocyst occurred in 8 patients with chronic pancreatitis, 2 patients with a tumor and 1 patients with acute pancreatitis (group 6). Malignant tumors were found in all 4 patients in group 4.

Widening of the duodenal loop and abnormalities of the mucosa were also frequently seen in patients without chronic pancreatic pathology.

The common bile duct was visualised in only 33 patients, with stenosis occurring in several patients with chronic pancreatitis and in one patient with a tumor of the pancreas.

Table II.5.3.1 Frequency of E.R.C.P. abnormalities in the head of the gland in each diagnostic group (1 to 7), (percentages).

| Item \ Group | 1 | 2 | 3 | 4 | 6 | 7 |
|---|---|---|---|---|---|---|
| n= | 18 | 20 | 9 | 4 | 17 | 7 |
| DUCT | | | | | | |
| Diameter increased | 67 | 63 | 22 | 33 | 41 | 29 |
| Contour vagueness | 59 | 53 | 33 | 33 | 6 | 29 |
| Caliber irregular. | 53 | 53 | 22 | 33 | 0 | 0 |
| Tortuosities | 35 | 26 | 0 | 33 | 0 | 0 |
| Concrements | 33 | 25 | 0 | 0 | 0 | 0 |
| DUCTULI | | | | | | |
| Diameter increased | 75 | 69 | 0 | 0 | 20 | 0 |
| Contour vagueness | 81 | 69 | 0 | 0 | 20 | 50 |
| Caliber irregular. | 69 | 63 | 50 | 0 | 0 | 0 |
| Tortuosities | 69 | 44 | 25 | 0 | 0 | 0 |
| Concrements | 44 | 19 | 0 | 0 | 0 | 0 |
| Opacities | 17 | 10 | 0 | 67 | 0 | 14 |
| Inflammatory tumor | 28 | 0 | 0 | 0 | 0 | 0 |
| Pseudocyst | 17 | 5 | 0 | 0 | 0 | 0 |
| Malignancy | 0 | 5 | 0 | 25 | 0 | 0 |
| Duct stenosis | 50 | 5 | 11 | 0 | 6 | 0 |
| Duodenal loop widened | 69 | 42 | 22 | 50 | 14 | 17 |
| Mucosal changes | 64 | 56 | 11 | 25 | 25 | 33 |

Table II.5.3.2 Frequency of E.R.C.P. abnormalities in the body of the gland in each diagnostic group (1 to 7), (percentages).

| Item \ Group | 1 | 2 | 3 | 4 | 6 | 7 |
|---|---|---|---|---|---|---|
| n= | 18 | 20 | 9 | 4 | 17 | 7 |
| DUCT | | | | | | |
| Diameter increased | 75 | 58 | 11 | 67 | 29 | 0 |
| Contour vagueness | 56 | 58 | 44 | 0 | 18 | 0 |
| Caliber irregular. | 75 | 47 | 11 | 0 | 0 | 14 |
| Tortuosities | 62 | 42 | 11 | 0 | 0 | 0 |
| Concrements | 50 | 20 | 0 | 0 | 0 | 0 |
| DUCTULI | | | | | | |
| Diameter increased | 80 | 67 | 33 | 0 | 20 | 0 |
| Contour vagueness | 87 | 93 | 33 | 0 | 10 | 0 |
| Caliber irregular. | 87 | 67 | 0 | 0 | 0 | 0 |
| Tortuosities | 87 | 53 | 0 | 0 | 0 | 0 |
| Concrements | 53 | 7 | 0 | 0 | 0 | 0 |
| Opacities | 0 | 26 | 11 | 0 | 6 | 29 |
| Inflammatory tumor | 6 | 5 | 0 | 0 | 0 | 0 |
| Pseudocyst | 6 | 5 | 0 | 0 | 0 | 0 |
| Malignancy | 0 | 0 | 0 | 0 | 0 | 0 |
| Duct stenosis | 22 | 10 | 0 | 67 | 12 | 0 |
| Duodenal loop widened | 23 | 11 | 22 | 0 | 7 | 0 |
| Mucosal changes | 14 | 19 | 0 | 0 | 0 | 0 |

Table II.5.3.3 Frequency of E.R.C.P. abnormalities in the tail of the gland in each diagnostic group (1 to 7), (percentages).

| Item \ Group | 1 | 2 | 3 | 4 | 6 | 7 |
|---|---|---|---|---|---|---|
| n= | 18 | 20 | 9 | 4 | 17 | 7 |
| DUCT | | | | | | |
| Diameter increased | 87 | 35 | 12 | 100 | 24 | 0 |
| Contour vagueness | 80 | 65 | 50 | 0 | 18 | 0 |
| Caliber irregular. | 87 | 59 | 12 | 0 | 12 | 0 |
| Tortuosities | 80 | 53 | 12 | 0 | 6 | 0 |
| Concrements | 40 | 17 | 0 | 0 | 0 | 0 |
| DUCTULI | | | | | | |
| Diameter increased | 92 | 50 | 50 | 0 | 15 | 0 |
| Contour vagueness | 92 | 88 | 0 | 0 | 15 | 0 |
| Caliber irregular. | 83 | 75 | 0 | 0 | 0 | 0 |
| Tortuosities | 83 | 62 | 0 | 0 | 0 | 0 |
| Concrements | 50 | 12 | 0 | 0 | 0 | 0 |
| Opacities | 12 | 22 | 25 | 0 | 29 | 29 |
| Inflammatory tumor | 24 | 6 | 0 | 0 | 0 | 0 |
| Pseudocyst | 12 | 0 | 0 | 33 | 6 | 0 |
| Malignancy | 0 | 0 | 0 | 75 | 0 | 0 |
| Duct stenosis | 18 | 5 | 0 | 50 | 0 | 0 |
| Duodenal loop widened | 38 | 12 | 0 | 75 | 7 | 0 |
| Mucosal changes | 15 | 12 | 0 | 0 | 0 | 0 |
| Common bile duct stenosis | 57 | 8 | 33 | 50 | 17 | 0 |

Table II.5.4 Number of E.R.C.P. films reviewed of each diagnostic group (1 to 7) and resulting diagnosis

| Group | Size*) | Diagnosis | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | CP 0 | CP I | CP II | CP III | CA | AP | PEPI |
| 1 | 18 | 0 | 1 | 4 | 13 | 0 | 0 | 0 |
| 2 | 20 | 1 | 6 | 3 | 9 | 0 | 1 | 0 |
| 3 | 9 | 4 | 1 | 0 | 0 | 0 | 0 | 4 |
| 4 | 4 | 0 | 0 | 0 | 0 | 4 | 0 | 0 |
| 6 | 17 | 15 | 0 | 0 | 0 | 0 | 2 | 0 |
| 7 | 7 | 7 | 0 | 0 | 0 | 0 | 0 | 0 |
| Total | 75 | 27 | 8 | 7 | 22 | 4 | 3 | 4 |

*) Number of E.R.C.P. films reviewed in each group.
CP 0 = Normal pancreatogram
CP I = Grade I chronic pancreatitis, see section II.5.1
CP II = Grade II chronic pancreatitis
CP III = Grade III chronic pancreatitis
Ca = Changes compatible with malignant tumor
AP = Changes compatible with acute pancreatitis
PEPI = Painless exocrine pancreatic insufficiency

II.5.2.3 Correlation between E.R.C.P. findings and clinical diagnosis in 75 patients.

Table II.5.4 presents the E.R.C.P. findings in 75 patients of various diagnostic groups (see II.2). Changes compatible with chronic pancreatitis were defined as has been outlined in table II.5.1 and graded into 3 categories. Changes indicating the presence of a malignant tumor were also described in table II.5.1 Acute pancreatitis was diagnosed in the presence of parenchymatous opacifications without ductal or ductular abnormalities. Painless exocrine pancreatic insufficiency was defined by a gracile main duct with minimal caliber irregularities but without ductular changes or other criteria of chronic pancreatitis.

A normal E.R.C.P. was seen in 26 patients, 21 of whom were also clinically diagnosed not to suffer from chronic pancreatic disease. In 4 patients of group 3 (suspected chronic pancreatitis) a normal E.R.C.P. was seen and in 1 patient of group 2.

Changes compatible with chronic pancreatitis were found on the E.R.C.P. of 37 patients, 36 of whom belonged to group 1 and 2 and 1 belonged to group 3. The majority of patients had grade III changes, indicating severe disease.

A malignant tumor was diagnosed by E.R.C.P. in all 4 patients with pancreatic cancer in whom the procedure had been carried out satisfactory.

Signs of acute inflammation, particularly parenchymatous opacifications, were seen in 3 patients, 1 in group 2 and 2 in group 6.

The changes reported to be associated with painless exocrine pancreatic insufficiency, i.e. a gracile duct with minimal caliber irregularities, were seen in all four patients in group 3 in whom this essentially clinical diagnosis had been made. See also section I.2.1.2.2 and II.2.2

Table II.5.5 Correlation between E.R.C.P. grading and severity of chronic pancreatitis expressed as number of factors in 36 patients.

| Number of factors | 0 | 1 | 2 | 3 | Total |
|---|---|---|---|---|---|
| E.R.C.P.grade | | | | | |
| CP 0 | - | 1 | - | - | 1 |
| CP I | 7 | - | - | - | 7 |
| CP II | 4 | 2 | 1 | - | 7 |
| CP III | 9 | 5 | 6 | 1 | 21 |
| Total | 20 | 8 | 7 | 1 | 36 |

### II.5.2.4 Correlation between E.R.C.P. grading and clincal severity of chronic pancreatitis.

The severity of chronic pancreatitis can be assessed by the presence of factors indicating advanced disease, like steatorrhoea, diabetes and pancreatic calcifications on the plain X-ray of the abdomen. See also table II.3.11 (section II.3.3). Table II.5.5 presents the correlation between the severity of chronic pancreatitis in 36 patients of whom sufficient data were available and the E.R.C.P. grading according to the method outlined in section II.5.1.2

Although only a minority of patients, even with advanced E.R.C.P. changes, had one or more factors indicating severe chronic pancreatitis, all but one patients with two or more factors had advanced E.R.C.P. changes.

Thus, the predictive value of the clinical condition with regards to the E.R.C.P. grade appears to be greater than the predictive value of E.R.C.P. for the clinical situation.

### II.5.2.5 Correlation between E.R.C.P. and the secretin-CCK test

#### II.5.2.5.1 Does E.R.C.P. impair the results of the secretin-test?

In section I.3.3.3 reference has been made to several publications regarding the harmful effects of the performance of E.R.C.P. on the exocrine pancreatic function. In order to find out whether E.R.C.P. procedures have possibly interfered with the secretin-CCK test in our series, we analysed the results of the test in patients who had had an E.R.C.P. performed either before or after the test. Overall, E.R.C.P. was performed in 87 patients who had undergone a secretin-CCK test. Although not all films were available for review, this was not considered a hindrance for this part of the analysis.

Table II.5.6 presents the proportions of abnormal secretin-CCK test results in patients who either had the E.R.C.P. performed before or after the test. The proportion of abnormal tests, particularly in patients without pancreatic disease, appears not to be increased by previous E.R.C.P.

Table II.5.6 Proportion of abnormal secretin-CCK test results related to the timing of E.R.C.P. in 87 patients

| | E.R.C.P. before test | | E.R.C.P. after test | |
|---|---|---|---|---|
| Group | Size | % abnormal*) | Size | % abnormal*) |
| 1 + 2 | 14 | 71 | 31 | 87 |
| 3 | 5 | 60 | 5 | 60 |
| 4 | 2 | 50 | 2 | 100 |
| 6 + 7 | 7 | 0 | 21 | 19 |
| Total | 28 | 50 | 59 | 61 |

N.B. Interval between E.R.C.P. and subsequent secretin-CCK test: 4-54 days, in half of the patients less than 1 week.
*) Percentage of abnormal secretin-CCK tests ($Z<0$).

#### II.5.2.5.2 Correlation of secretin-CCK test parameters and E.R.C.P. items

Correlation coefficients between individual secretin-CCK test parameters and E.R.C.P. items were calculated for all 75 patients, for each part (head, body and tail) of the pancreas. Table II.5.7.1-3 present only the correlations with a Pearson coëfficiënt > 0.40.

Of the basal secretin-CCK test parameters, only chymotrypsin concentration was correlated with ductular E.R.C.P. items in head and body.

Peak and total volume showed hardly any relevant correlations with E.R.C.P. items. Enzyme concentrations and outputs showed more correlations with E.R.C.P. items than bicarbonate concentrations and outputs. Particularly chymotrypsin output had many correlations with ductular E.R.C.P. items.

There were more relevant correlations between secretin-CCK test parameters and E.R.C.P. items of the body (40) of the gland than of the tail (29) and head (20).

Hardly any relevant correlations were found between test parameters and items regarding space occupying lesions and duodenal changes. These figures are not presented in the table.

### II.5.2.5.3 Comparison of secretin-CCK test results with E.R.C.P. results.

Finally, after calculating correlations between individual secretin-CCK test parameters and E.R.C.P. items, the results of both procedures for each patient will be compared.

The E.R.C.P. results are expressed as grades of severity of chronic pancreatitis, see section II.5.1. Grade I means changes of the side branches only, grade II means changes of main duct and grade III represents the presence of complications like a fistula or pseudocyst. The results of the secretin-CCK test are expressed as the Z-score, the value which was obtained by substitution of the parameters of the allocation rule (see section II.3.2.4).

In the group of 38 patients with chronic pancreatitis of whom E.R.C.P. films were reviewed, 37 had E.R.C.P. changes compatible with chronic pancreatitis of varying severity; in one patient the E.R.C.P. showed signs of acute inflammation. Table II.5.8.1 presents the Z-scores of the secretin-CCK test compared to E.R.C.P. grades in these patients. Of the patients with mild and moderate E.R.C.P. changes (grade I and II) the majority had an intermediate Z-score of the secretin-CCK test, while the majority of patients with severe E.R.C.P. changes (grade III) had a low Z-score, indicating severe impairment of the exocrine pancreatic function. The only patient with a normal E.R.C.P. also had a normal secretin-CCK test.

The data of patients without chronic pancreatic disease (group 6 and 7) are presented in table II.5.8.2. Out of 24 patients, 2 had signs of acute pancreatitis on the E.R.C.P., one of whom had an abnormal secretin-CCK test ($Z<0$). Of the 22 patients with a normal E.R.C.P., 19 had a normal secretin-CCK test ($Z>0$).

When the results of both the secretin-CCK test and the E.R.C.P. are expressed as either normal or abnormal, and the patients pancreatitis in group 1 and 2 and the patients in group 6 and 7 are pooled in 2 groups, the following relationship between both modalities is obtained (see table II.5.9).

Table II.5.7.1 Correlation coëfficiënts between secretin-CCK test parameters and E.R.C.P.items in 75 patients Head of the pancreas

| E.R.C.P. | Duct | | Ductuli | | | |
|---|---|---|---|---|---|---|
| | contour | caliber | contour | caliber | tortuos | concrem |
| S-CCK parameters | | | | | | |
| b.v. | | | | | | |
| b.b.c. | | | | | | |
| b.c.c. | | -.40 | | -.42 | -.43 | |
| p.v. | | | | | | |
| p.b.c. | | | | | -.46 | |
| p.b.o. | | | | | -.50 | |
| p.c.c. | | | -.48 | -.52 | -.44 | |
| p.c.o. | | | | -.50 | -.49 | -.42 |
| t.v. | | | | | | |
| m.b.c. | | | | | -.53 | |
| t.b.o. | | | | | -.50 | |
| m.c.c. | | | -.51 | -.55 | -.48 | |
| t.c.o. | | | -.42 | -.51 | -.51 | -.41 |

Legend:-for interpretation abbreviations secretin-CCK parameters see table II.3.1
-for abbreviations E.R.C.P. items see table II.5.1

Table II.5.7.2 Correlation coëfficiënts between secretin-CCK test parameters and E.R.C.P. items, 75 patients Body of the pancreas.

| E.R.C.P. | Duct | | Ductuli | | | |
|---|---|---|---|---|---|---|
| | contour | caliber | contour | caliber | tortuos | concrem |
| S-CCK parameters | | | | | | |
| b.v. | | | | | | |
| b.b.c. | | | | | | |
| b.c.c. | | -.41 | | -.50 | -.46 | |
| p.v. | -.40 | | | | | -.44 |
| p.b.c. | | | | | | -.44 |
| p.b.o. | | | | -.42 | -.40 | -.44 |
| p.c.c. | | | | -.48 | -.47 | -.42 |
| p.c.o. | -.48 | -.44 | -.47 | -.58 | -.58 | -.51 |
| t.v. | | | | | | -.48 |
| m.b.c. | | | | -.44 | -.40 | -.42 |
| t.b.o. | | | | -.44 | -.42 | -.45 |
| m c.c. | -.39 | | -.46 | -.55 | -.52 | -.43 |
| t.c.o. | -.44 | | -.44 | -.55 | -.54 | -.51 |

Legend: for interpretation abbreviations secretin-CCK parameters see table II.3.1
for abbreviations E.R.C.P. see table II.5.1

Table II.5.7.3 Correlation coëfficiënts between secretin-CCK test parameters and E.R.C.P. items, 75 patients. Tail of the pancreas.

| E.R.C.P. | Duct | | Ductuli | | | |
|---|---|---|---|---|---|---|
| | contour | caliber | diameter | contour | caliber | tortuos |
| S-CCK parameters | | | | | | |
| b.v. | | | | | | |
| b.b.c. | | | | | | |
| b.c.c. | | | -.46 | | | |
| p.v. | | | | | | |
| p.b.c. | | | | | | -.41 |
| p.b.o. | -.42 | | | | | -.43 |
| p.c.c. | -.51 | -.44 | | | -.41 | -.44 |
| p.c.o. | -.54 | -.45 | -.46 | -.42 | -.42 | -.40 |
| t.v. | | | | | | |
| m.b.c. | -.47 | | | | | -.49 |
| t.b.o. | | | | | | -.45 |
| m.c.c. | -.58 | -.45 | -.42 | -.45 | -.45 | -.50 |
| t.c.o. | -.53 | -.44 | -.49 | -.43 | -.40 | -.46 |

Legend: for interpretation abbreviations secretin-CCK parameters see table II.3.1
for abbreviations E.R.C.P. see table II.5.1

Out of 23 patients with a normal E.R.C.P., 20 had a normal secretin- CCK test; out of 36 patients with signs of chronic pancreatitis on the E.R.C.P., 30 had an abnormal secretin-CCK test; thus in 50 out of 59 patients (85%), E.R.C.P. and secretin-CCK test results coincided. A normal secretin-CCK test with an abnormal E.R.C.P. was found in 6 patients (10%) and the reverse, an abnormal secretin-CCK test with a normal E.R.C.P. was seen in 3 patients (5%). The difference between these two figures is not statistically significant (McNemar's test, p=0.51).

Table II.5.8.1 Comparison of Z-score of secretin-CCK test with E.R.C.P. grade in 37 patients with chronic pancreatitis.

| E.R.C.P. grade | 0 | I | II | III | Total |
|---|---|---|---|---|---|
| Z-score S-CCK test | | | | | |
| Z>0 | 1 | 2 | 2 | 2 | 7 |
| 0>Z>-1 | - | 3 | 2 | 6 | 11 |
| -1>Z>-2 | - | 2 | 3 | 10 | 15 |
| -2>Z | - | - | - | 4 | 4 |
| Total | 1 | 7 | 7 | 22 | 37 |

Table II.5.8.2 Comparison of Z-score of secretin-CCK test with E.R.C.P. grade in 24 patients without chronic pancreatic disease

| E.R.C.P.grade | 0 | CP | AP | Total |
|---|---|---|---|---|
| Z-score S-CCK | | | | |
| Z>0 | 19 | - | 1 | 20 |
| Z<0 | 3 | - | 1 | 4 |
| Total | 22 | - | 2 | 24 |

Legend: Z-score = value obtained by substitution of allocation rule
0 = Normal E.R.C.P.
CP = Chronic pancreatitis (grade I, II or III)
AP = Acute pancreatitis

Table II.5.9 Comparison of secretin-CCK test results with the results of E.R.C.P. in 59 patients with and without chronic pancreatitis

| E.R.C.P. | Normal | CP | Total |
|---|---|---|---|
| Secretin-CCK test | | | |
| Normal ($Z>0$) | 20 | 6 | 26 |
| Abnormal ($Z<0$) | 3 | 30 | 33 |
| Total | 23 | 36 | 59 |

II.5.3 Evaluation of E.R.C.P. results.

The E.R.C.P. films in this study were reviewed using a protocol designed according to Kasugai (Kasugai, Kuno et al, 1972) but modified so as to employ as binary recording system. In this protocol the hypothesis is incorporated that in chronic pancreatitis ductular changes precede ductal changes (Nakamura, Sarles & Payan, 1972). Similar protocols have been used by others but without the binary recording system (Braganza, Hunt & Warwick, 1982).

A grading system of severity of E.R.C.P. changes in chronic pancreatitis was also devised by us, based on the same presumptions, that ductular changes (grade I) represent less severe chronic pancreatitis than ductal changes (grade II) and that signs like calcifications and fistulae represent advanced disease (grade III).

It appeared that a majority of patients with histologically confirmed chronic pancreatitis (group 1, see II.2) had E.R.C.P. changes grades II and III, while patients with chronic pancreatitis diagnosed by other means (group 2) had a more even distribution of various grades of lesions on E.R.C.P.

Correlation of E.R.C.P. grade with the number of factors indicating advanced chronic pancreatitis indicated that E.R.C.P. is a much more sensitive indicator of chronic pancreatic disease than is the clinical assessment as expressed by the number of positive factors. When these figures are compared with those of the correlation between secretin-CCK test results and number of positive factors (see section II.3.3), there appears to be no great difference between the sensitivity of secretin-CCK test and E.R.C.P. with regards to the assessment of the severity of chronic pancreatitis.

Analysis of the E.R.C.P. data was performed in order to gain more insight in the relevance of individual items and into the

relationship between morphological (E.R.C.P.) changes and functional (secretin-CCK test) impairment in chronic pancreatitis.

Intercorrelation of E.R.C.P. items was analysed first and demonstrated a multitude of correlations without clearly identifying two or more independent sets of items.

Subsequently, the frequency with which certain E.R.C.P. changes occurred in various groups of patients was analysed. This resulted in the identification of certain 'hard' items concerning the diagnosis of chronic pancreatitis. In the interpretation of these data it should be born in mind again that E.R.C.P. had been used in the classification of patients into various diagnostic groups (section II.2). Therefore, the diagnostic performance of E.R.C.P. was not assessed, as it would have been severely biased by this selection procedure.

Correlation of individual secretin-CCK test parameters with E.R.C.P. items demonstrated several interesting features. On the whole, secretin-CCK test parameters, particularly concentrations and outputs of chymotrypsin and bicarbonate, did correlate more closely with ductular than with ductal items. Furthermore, correlations between secretin-CCK test parameters and E.R.C.P. items were more often highly significant in the body of the gland than in the head and tail. Parameters of hydraletic secretion, particularly peak bicarbonate output, did not show correlations with E.R.C.P. items that were not also shown for parameters of ecbolic response, particularly mean chymotrypsin concentration. Thus, the different sites of secretion of both components (acini for enzymes and ductular epithelium for bicarbonate) could not be recognised in E.R.C.P. items.

Comparison of the results of E.R.C.P. (expressed as grades) and the secretin CCK test (expressed by the Z-score of the allocation rule, see section II.3.2.4), demonstrated a good relationship between both modalities. This was also shown when the results of both procedures were excpressed as normal or abnormal. A compatibility rate of 85% is in accordance with the literature (see section I.3.4 and table I.10).

## II.6 THE SECRETIN-CCK TEST AND HISTOLOGY IN CHRONIC PANCREATITIS.

### II.6.1 Material and methods.

All patients in group 1 (n=25) had been submitted to various types of pancreatic surgery, mainly resections (distal or total pancreatectomy, partial pancreatoduodenectomy or Whipple's resction), for chronic pancreatitis. The indications varied from intractable pain to complications like pseudocyst, fistula formation and bleeding into the pancreatic duct.

Routine histological examinations have been performed on the tissue resected or biopsied at operation. Usually 3 or 4 different sections have been prepared, representing various parts of the specimen.

For the purpose of this study, the available sections of the 25 patients included in group 1 (see chapter II.2) were reviewed by an experienced pathologist, using a protocol designed specially for this purpose, see table II.6. The protocol was designed in accordance with the reports by Sarles and coworkers on the histological findings in chronic pancreatitis (Nakamura, Sarles & Payan, 1972; Sarles & Sahel, 1976). The items were checked one by one and abnormalities were recorded in a semi-quantitative scale (none, mild, moderate or severe).
The following statistical procedures were used in this part of the study. Levels of significance for the correlation coefficients were assessed by the formula:

$$t = r \left| \frac{n-2}{1-r^2} \right|^{\frac{1}{2}}$$

r = Pearson correlation coefficient
n = number of individuals

This test statistic has a t-distribution with n-2 degree of freedom.

### II.6.2 Results

#### II.6.2.1 Frequency of histological findings.

Table II.6.2 presents the frequency and severity of the histological findings in 25 patients with chronic pancreatitis. In 1 patient, operated because of a pseudocyst, not sufficient pancreatic tissue was available to allow an opinion on the main duct.

Table II.6 Protocol for reviewing histological material of patients with chronic pancreatitis.

| Items | Severity | | | |
|---|---|---|---|---|
| | Absent | Mild | Moderate | Severe |
| PARENCHYMA | | | | |
| Cellular changes | | | | |
| Atrophy | | | | |
| Inflammation- round cells | | | | |
| polymorphs | | | | |
| Fibrosis- intralobular | | | | |
| - interlobular | | | | |
| DUCTAL SYSTEM | | | | |
| Intralobular- dilatation | | | | |
| Interlobular- dilatation | | | | |
| - hyperplasia | | | | |
| - plugging | | | | |
| - calcifications | | | | |
| Main duct- dilatation | | | | |
| - hyperplasia | | | | |
| - plugging | | | | |
| clacifications | | | | |
| ARTERIOSCLEROSIS | | | | |
| NERVE CELLS | | | | |
| Number increased | | | | |
| Perineural inflammation | | | | |
| Intraneural degeneration | | | | |
| ISLETS OF LANGERHANS | | | | |
| Abnormal aspect. | | | | |

Atrophy was present to various degrees in all but 1 patient, who had only cellular changes with vacuolisation and round cell infiltration.

The amount of fibrosis, both intra- and interlobular, was closely correlated to the degree of atrophy in the majority of patients.

Inflammatory reaction, either round cells or, less frequently, polymorphonuclear cells, was noted in all but one patient, but the degree did not correlate with the amount of atrophy and fibrosis.

Dilatation of the small ducts (intra- and interlobular) was seen in all but one patient and considered minimal in another one.

Main duct dilatation was seen less frequently and its frequency was not related to that of small duct dilatation.

Hyperplasia of ductal and ductular epithelium was seen in only six patients with varying degrees of dilatation.

Formation of protein plugs in the lumen of the main duct or its branches was present in 14 of the patients.

Calcifications, recorded as present or absent, were found in more than half of the cases.

Table II.6.2 Summary of histological findings in 25 patients submitted to surgery for chronic pancreatitis.

| Item \ Severity | Absent | Mild | Moderate | Severe | Total |
|---|---|---|---|---|---|
| Atrophy | 1 | 6 | 7 | 11 | 25 |
| Small duct dilatation | 1 | 10 | 10 | 4 | 25 |
| Main duct dilatation | 4 | 8 | 7 | 5 | 24*) |
| Inflammation | - | 18 | 5 | 2 | 25 |
| Fibrosis | 1 | 4 | 5 | 15 | 25 |
| Hyperplasia | 19 | 3 | 2 | 1 | 25 |
| Plugging | 11 | 10 | 4 | - | 25 |
| Calcifications | 16 | | 9 | | 25 |
| Arteriosclerosis | 7 | 7 | 7 | 4 | 25 |
| Nerve cell proliferation | 9 | 12 | 4 | - | 25 |

II.6.2.2 Correlation between the secretin-CCK test and histology

The secretin-CCK test results of 22 of the 25 operated patients were abnormal, see section II.3.3. A comparison of the histological findings in the 3 patients with a normal test with the findings in the 22 patients with an abnormal test showed that moderate or severe atrophy, fibrosis and small duct

dilatation occurred exclusively in patients with an abnormal secretin-CCK test. One patient with a normal secretin-CCK test had a moderately dilated main duct on histological examination. The 3 patients with a normal secretin-CCK test all demonstrated mild histological changes of chronic pancreatitis. One patient had no atrophy, one had minimal and one had mild atrophy; similarly, fibrosis was absent in one, minimal in one and mild in the third patient. Dilatation of the intralobular ductuli was present in none, dilatation of the interlobular ducts was mildly present in 2 of the 3 patients with a normal secretin-CCK test. A mild degree of plug formation occurred in 1 patient; calcifications and nerve cell changes were not seen in these 3 cases. See table II.6.3

Thus, it appears that patients with a normal secretin-CCK test result had all 3 minimal or mild histological changes, whereas moderate and severe changes were seen only in patients with an abnormal test result.

Table II.6.3 Correlation between results of the secretin-CCK test and severity of histological findings in 25 patients with chronic pancreatitis.

| | | Secretin-CCK test result | | |
|---|---|---|---|---|
| | | Normal | Abnormal | Total |
| Histology | | | | |
| Atrophy | Absent/mild | 3 | 4 | 7 |
| | Moderate/severe | 0 | 18 | 18 |
| Fibrosis | Absent/mild | 3 | 2 | 5 |
| | Moderate/severe | 0 | 20 | 20 |
| Main duct dilatation | Absent/mild | 1 | 11 | 12 |
| | Moderate/severe | 1 | 11 | 12 |
| Small duct dilatation | Absent/mild | 3 | 8 | 11 |
| | Moderate/severe | 0 | 14 | 14 |

Correlation coefficients were calculated between the individual secretin-CCK test parameters that had been selected by discriminant analysis, see section II.3.2.4, and the severity of the histological items. Similarly, correlation coefficients between the Z-score of the allocation rule of the secretin-CCK test and the severity of the histological items were calculated. The results are presented in table II.6.4 and show statistically significant correlations between the test parameters, particularly peak bicarbonate output, and the severity of several histological items, notable strophy, small and main duct dilatation and nerve cell proliferation. No statistically significant correlations were found between secretin-CCK test parameters and the degree of arteriosclerosis.

Table II.6.4 Pearson's correlation coefficients between severity of histological changes and individual secretin-CCK test parameters in 25 patients with chronic pancreatitis.

| | Atrophy | Small duct dilatation | Main duct dilatation | Nerve cell proliferat |
|---|---|---|---|---|
| S-CCK parameters | | | | |
| p.v. | -.44 | -.30 | -.45 | |
| p.b.o. | -.71 | -.68 | -.41 | -.51 |
| m.c.c. | -.57 | -.46 | -.22 | -.41 |
| Z-score | -.62 | -.58 | -.32 | -.49 |

Legend: p.v. peak volume
p.b.o. peak bicarbonate output
m.c.c. mean chymootrypsin concentration

### II.6.2.3 Correlation between histological findings and E.R.C.P.

E.R.C.P. was attempted in 23 of the patients who were operated on for chronic pancreatitis. E.R.C.P. failed to visualise the main pancreatic duct in 4 cases and the films of 1 patient were not available for review. Thus, the results of E.R.C.P. could be correlated with the histological findings in 18 patients.

Table II.6.5 presents the comparison of E.R.C.P. grades (see section II.5.1.2) with the degree of atrophy. One patient, with a pseudocyst on E.R.C.P., had no atrophy, while 2 other patients with a pseudocyst had mild atrophy on histological examination. Moderate and severe atrophy was seen in 13 patients and all had grade II or III E.R.C.P. changes.

Table II.6.5 Correlations between atrophy on histological examination and E.R.C.P. grade in 18 patients with chronic pancreatitis.

| | Degree of atrophy | | | |
|---|---|---|---|---|
| | None | Mild | Moderate | Severe |
| E.R.C.P.grade | | | | |
| I | - | 1 | - | - |
| II | - | 1 | 1 | 3 |
| III | 1 | 2 | 5 | 4 |

Small duct dilatation was absent in 1 and minimal in 2 patients with a pseudocyst. Five patients with mild dilatation of the small ducts on histology had main duct changes on E.R.C.P. (grade II) and the only patient with E.R.C.P. grade I changes (i.e. only ductular changes) had moderate dilatation of the small ducts. The remaining 9 patients with moderate and severe small duct dilatation all had E.R.C.P. grade III changes (see table II.6.6).

Table II.6.6 Correlations between small duct dilatation and E.R.C.P. grade in 18 patients with chronic pancreatitis.

| | Degree of small duct dilatation | | | |
|---|---|---|---|---|
| | None | Mild | Moderate | Severe |
| E.R.C.P.grade | | | | |
| I | - | - | 1 | - |
| II | - | 5 | - | - |
| III | 1 | 2 | 7 | 2 |

Assessment of main duct diameter on histological examination was possible in the section of 16 patients, 3 of whom had no dilatation: 1 had ductular changes only on E.R.C.P. and 2 had a pseudocyst, table II.6.7. The other 13 patients had mild to severe dilatation of the main duct on histological examination and all had grade II or III E.R.C.P. changes.

Table II.6.7 Correlation between histological dilatation of the main duct and E.R.C.P.grade in 16 patients with chronic pancreatitis.

| | Degree of main duct dilatation | | | |
|---|---|---|---|---|
| | None | Mild | Moderate | Severe |
| E.R.C.P.grade | | | | |
| I | 1 | - | - | - |
| II | - | 2 | 1 | 1 |
| III | 2 | 2 | 3 | 4 |

II.6.3 Evaluation of the results of histological examination.

Histological material obtained by surgical procedures of 25 patients with chronic pancreatitis was reviewed according to a specially designed protocol, that was based on the findings reported in the literature (Nakamura, Sarles & Payan, 1972; Sarles & Sahel, 1976). It should be emphasised that the available material had been prepared for routine histological examination of the resected or biopsied tissue and was therefore not necessarily representative of the ongoing disease process.

The frequency of the recorded abnormalities were compatible with the findings reported by other authors (Nakamura, Sarles & Payan, 1972; Sarles, Sahel et al, 1976). Atrophy, fibrosis, both intra- and interlobular, dilatation of the main duct and side branches with and without plug formation and calcifications were found to be present in these patients with chronic pancreatitis, in a so called lobular distribution (Sarles & Sahel, 1976). Inflammatory reaction, both round cells and polymorphonuclear cells, was inconstant and not related to the degree of atrophy and fibrosis. This supports findings of others, who have questioned whether the inflammatory component of chronic pancreatitis is really important (Vennes, 1982). Plug formation, calcifications and nerve cell changes were found in many patients. Changes in intrapancreatic nerve cells, both histological and biochemical, have been reported in alcoholic dogs (Sarles, Sahle et al, 1980). The histological changes in that study comprise of perineural inflammatory reaction and intraneural degeneration, whereas histochemical studies demonstrated an increase in acetyl choline transferase, indicating an increased synthesis of the transmitter (Sarles, Sahel et al, 1980).

In the present study an increase in the number of intrapancreatic nerve fibers was evident to the experienced observer, although no quantitative measurements were done. The degree of nerve cell proliferation was not correlated to the degree of atrophy, therefore it is unlikely that the increase in nerve cells was apparent only because of the loss of parenchyma. It is not known whether these nerve fibers are sympathetic or parasympathetic and further study is required to elucidate their character and their role in chronic pancreatitis. See also chapter I.2.1.2.1.

Peak bicarbonate output and (to a lesser degree) mean chymotrypsin concentration appeared to be inversely related to the degree of atrophy, small duct dilatation and nerve cell proliferation. Also, the Z-score, resulting from the allocation rule that was obtained by discriminant analysis of the secretin-CCK test, showed an inverse correlation with histological items. As there are no reports in the accessible literature on the correlation between secretin-CCK parameters and histological

items in chronic pancreatitis, we cannot compare these findings with the results of others.

First, it has to be noted that the correlation coefficients are not very high. It is therefore possible that the correlations are merely coincidental.

Second, it is not explained why the correlation coefficients between mean chymotrypsin concentration (the 'best' parameter according to discriminant analysis) and histological items are lower than those between peak bicarbonate concentration (the second 'best' parameter) and histological items.

The 3 patients who had a normal secretin-CCK test out of the 25 operated because of chronic pancreatitis, all had minimal or mild histological changes when compared to the other patients. Here again, a clear relationship is found between functional impairment and morphological changes.

When correlations are looked for in this way, it should be noted that the histological examinations were performed upon tissue resected because it was considered to be the most severely affected part of the pancreas, and therefore not necessarily representative of the functional capacity of the gland. This difficulty however, is inherent to the analysis of pancreatic histology in man, as total pancreatectomy for chronic pancreatitis is hardly justifiable (Gebhardt, Gall et al, 1979). Another problem that is not easily solved is the fact that in chronic pancreatitis, lesions are not evenly distributed but differ in severity form one lobule to the other, the so called lobular distribution. Quantification of histological abnormalities has to pay respect to this uneven distribution by taking into account the whole specimen. In our study only routine sections were available for review. Thus, a systematic examination of the resected specimen was not really possible.

The number of reports on the relationship between exocrine pancreatic function impairment and histology in chronic pancreatitis is very limited. Adler and coworkers found the relationship between exocrine secretion and histology to be frequently discordant (Adler, Waye & Dreiling, 1976). Several experimental studies have neither been able to establish clear cut relations between structure and function in chronic pancreatitis (Sarles & Sahel, 1976).

Correlations between histological changes and E.R.C.P. results were also investigated. The degree of pancreatographic changes was correlated with the degree of changes of the items: atrophy, small and main duct dilatation. There appeared to be a relationship between the severity of E.R.C.P. findings, expressed in grades, and the degree of histological changes, but the numbers were too small for reliable statistical analysis.

These results do not point to a direct correlation between the findings of E.R.C.P. and histological items. It is interesting that there are no reports in the literature on this subject. Even the often quoted paper by Kasuagai and coworkers,

in which the E.R.C.P. changes of chronic pancreatitis are classified, is based on patients who had been only sporadically submitted to surgery. Instead they were selected and classified according to the clinical findings (Kasugai, Kuno et al, 1972).

It might be argued that the distribution of E.R.C.P. changes was too skewed (1 patient grade I, 5 patients grade II and 12 patients grade III) to detect a linear correlation. It is therefore not allowed to draw too hard a conclusion from these data, but it remains striking that better correlations were found between secretin-CCK test parameters and histological items than between E.R.C.P. results and histological findings.

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# III GENERAL DISCUSSION

## III.1 EVALUATION OF THE ROLE OF THE SECRETIN-CCK TEST IN THE DIAGNOSIS OF CHRONIC PANCREATITIS AND PANCREATIC CANCER

Chronic pancreatitis is characterised by permanent functional and structural damage of the gland by the inflammatory process (Sarles, 1965). From this definition, several criteria have been derived for the clinical diagnosis of chronic pancreatitis:

- The demonstration of histological changes
- The presence of pancreatic calcifications on the plain X-ray
- Demonstration of impaired exocrine pancreatic function (Creutzfeldt, Fehr & Schmidt, 1970; Wakasugi, Funakoshi & Ibayashi, 1982).

In the past few years, the demonstration of typical changes on endoscopic retrograde cholangiopancreatography has also been generally accepted as evidence for the existence of chronic pancreatitis (Kasugai, Kuno et al, 1972; Braganza, Hunt & Warwick, 1982; Seligson, Cho et al, 1982)

Criteria for the assessment of severity of chronic pancreatitis have not been defined, but is generally accepted that the presence of pancreatic calcifications, steatorrhoea and diabetes are indicators of advanced disease (Sarles, Sahel et al, 1979; Bernades, Belghiti et al, 1983). No unanimity however, exists about the radiological and functional changes in early chronic pancreatitis (Gaucher, Bigard et al, 1981; Gowland, Kalantzis et al, 1981; Ruddell, Lintott & Axon, 1983). Thus, the selection and classification of patients with chronic pancreatitis appears only reliably possible in advanced stages of the disease. This is especially true for studies in which diagnostic procedures are analysed. Obviously, the more advanced the disease is with respect to destruction of parenchyma, the more easily it is identified by a host of test methods. This should be kept in mind when diagnostic procedures for chronic pancreatitis are compared.

In the present study, chronic pancreatitis had been diagnosed in 63 patients. Criteria for this diagnosis were: histology (25 patients), pancreatic calcifications (13 patients) and E.R.C.P. changes (25 patients). The frequency of factors indicating the presence of advanced chronic pancreatitis (diabetes, steatorrhoea and pancreatic calcifications) was comparable to that in several other series (Sarles, Sahel et al, 1979; Bernades, Belghiti et al, 1983; table I.11).

To assess the diagnostic performance of the secretin-CCK test in chronic pancreatic disease (i.e. chronic pancreatitis and pancreatic cancer), a group of subjects was used as controls that was comparable in many respects to the patient groups. These subjects had signs and symptoms that appeared to warrant

an investigation that was rather extensive in many instances, but that did not yield an organic diagnosis.

Comparison of the secretin-CCK test results of patients with chronic pancreatitis and without organic disease was done with the help of discriminant analysis. Using this statistical method we selected 2 parameters with a high discriminatory capacity and subsequently constructed an allocation rule that incorporated both parameters. The error rate of this allocation rule in the classification of patients with and without chronic pancreatitis was 15%. This result was verified by prospective analysis on split groups. Thus, application of the allocation rule to a new population of subjects will probably not lead to a significantly lower diagnostic performance. The diagnostic performance of the secretin-CCK test was in accordance with, or better than reports in the literature (table I.10):

- sensitivity 82%
- specificity 88%
- positive predictive value 69%
- negative predictive value 94%
- accuracy rate 86%

Separate analysis of diabetic patients without chronic pancreatitis did not lend support to the hypothesis that impaired exocrine pancreatic function is seen more often in diabetics than in nondiabetics without pancreatic disease, but the number of patients with insulin dependent diabetes was rather small in our series (Chey, Shay and Shuman, 1963; Baron & Navarro, 1973; Frier, Saunders et al, 1976).

Furthermore, no indications were found in our patients without chronic pancreatic disease that various types of gastric surgery (truncal vagotomy, highly selective vagotomy, gastrectomy) impaired the results of the secretin-CCK test, unless the anatomical situation of the gastrointestinal tract had been grossly altered so as to interfere with the sampling of duodenal contents.

Evidence was found that a recent attack of acute pancreatitis led to significantly more impaired secretin-CCK test results than could be exspected in patients with acute pancreatitis in the past. It seems therefore advisable not to perform the test within a period of 6 weeks after an acute attack, as the results may not be reliable within this period (Howat & Braganza, 1979; Mitchell, Playforth et al, 1983).

Finally, it was found that the results of the secretin-CCK test were abnormal in several malnourished patients without chronic pancreatic disease. This fact has been reported before (Gyr, Wolf et al, 1975).

A tumor of the pancreas had been diagnosed in 11 of out patients, confirmed by laparotomy and histology in all but 1. The tumor was found to be irresectable in 9 patients. This high incidence of advanced pancreatic cancer is characteristic for the 'dismal disease' (Fitzgerald, 1976). Again, it means that the diagnostic performance of a procedure for pancreatic cancer is dependent on the stage of the disease. Most authors do not state the stage of the tumor in their patients.

The performance of the test in pancreatic cancer could not be assessed reliably because the number of patients with a tumor was too small to allow separate discriminant analysis.

In summary, the diagnostic performance of the secretin-CCK test, interpreted with the aid of discriminant analysis, was found to be sufficiently high for us to propagate its use for the investigation of patients with suspected nonacute pancreatic disease. Falsely abnormal results can be exspected in patients with a recent episode of acute pancreatitis, in severely ill and/or malnourished patients and in patients with previous gastric surgery that has grossly altered the local anatomy, e.g. Roux-en-Y reconstruction.

## III.2 Comparison of the secretin-CCK test with other diagnostic procedures, particularly E.R.C.P.

In the patients of this series various radiological procedures had been performed, which provided the opportunity to compare the results of these procedures with those of the secretin-CCK test.

Plain films of the upper abdomen were made of most patients and showed pancreatic calcifications in more than one third of the patients with chronic pancreatitis and in 18% of the patients with a tumor of the pancreas. The presence of pancreatic calcifications is evidence of serious pathology: usually it indicates the presence of chronic pancreatitis but not seldom cancer of the pancreas. Thus, the demonstration of pancreatic calcifications calls for further analysis to elucidate the nature of the underlying pathology.

Hypotonic duodenography appeared to be of little value in the diagnosis of pancreatic disease in this study.

Ultrasonography had been performed in more than 75% of our patients. This procedure was introduced during the time of observation and experience gradually increased. This may account for the fact that the failure rate was fairly high (20%), but even in expert hands the imaging of the whole pancreas remains one of the most demanding exercises in ultrasonography (Pietri & Sahel, 1979). The diagnostic performance of ultrasonography in patients with chronic pancreatitis was not impressive but in pancreatic cancer abnormalities were detected in almost 90% of the patients without technical failures.

Computed tomography was introduced in this hospital towards the end of the observation period and only a small number of patients had been examined by this modality. As this procedure carries little or no risk to the patient and showed a high diagnostic performance both in chronic pancreatitis and in pancreatic cancer, its future role in the investigation of pancreatic disease appears rather promising (Goldberg, Glazer & Axel, 1981; Gore, Moss & Margulis, 1982).

Angiography has a limited place in the diagnosis of pancreatic disease. It is generally indicated only as a preoperative examination in chronic pancreatitis to recognise anatomical variations of the arteries of the upper abdomen (Thompson,

Eckhauser et al, 1981) and as a staging procedure to asess resectability in pancreatic cancer (Moossa, 1982; Obertop, Bruining et al, 1982).

Endoscopic retrograde cholangiopancreatography carries some risks, particularly acute pancreatitis, to the patient and requires expert endoscopists and radiologists for its execution. Therefore, it is generally agreed to perform this procedure only on strict indications, i.e. after other procedures have demonstrated the presence of pancreatic disease and essentially only when the results will have therapeutic consequences. Even in experienced hands the failure rate was 14% in our series, while the duct could be visualised in only half of the patients with cancer of the pancreas.

The interpretation of E.R.C.P. films is not always straightforward. Several opinions exist on the meaning of ductular changes without ductal abnormalities : some authors doubt their relevance (Gowland, Kalantzis et al, 1981; Ruddell, Lintot & Axon, 1983), others look upon them as the first signs of chronic pancreatitis (Kasugai, Kuno et al, 1972). Particularly the interpretation of these mild changes appears to cause differences of opinion (Gaucher, Bigard et al, 1981). Although the view that early E.R.C.P. changes in chronic pancreatitis occur only in the side branches is supported by the microscopical findings (Sarles, Sahel et al, 1976), no systematic analysis has been published of the relationship between pancreatographical and histological changes in chronic pancreatitis. Even in the 'classic' paper by Kasugai, patients were classified on the basis of clinical data (Kasugai, Kuno et al, 1972). In a report on the pancreatographic development of lesions in chronic pancreatitis, histology was obtained in only 7 out of 31 patients (Nagata, Homma et al, 1981).

In this study the relationship between E.R.C.P. and secretin-CCK test was explored first. Statistically siginificant correlations between individual secretin-CCK test parameters, especially chymotrypsin concentration and output, and E.R.C.P. items were found, particularly in the body and tail of the gland. Second, the final results of both procedures were compared and appeared to coincide in 85% of the patients with

and without chronic pancreatitis. When the secretin-CCK test was normal, 77% of the E.R.C.P.'s was normal as well and when the secretin-CCK test was abnormal, 91% of the E.R.C.P.'s was also abnormal. This predictability rate has to be related to the fact that patients were, at least in part, selected on the basis of the E.R.C.P. results. These results are in accordance with the literature, where also never a 100% coincidence of both procedures has been reported (Salmon, Baddeley et al, 1975; Dobrilla, Fratton et al, 1976; Nakano, Horiguchi et al, 1976; Rolny, Lukes et al, 1978; Otte, 1979; Tympner, Schaffner et al, 1979; Valentini, Cavallini et al, 1981). Several explanations may be given for this divergence.

First, E.R.C.P. might be more sensitive than the secretin-CCK test, detecting chronic pancreatitis in an earlier stage. Although this might appear likely, it should be remembered that in many studies, like the present one, patients had been selected on the basis of E.R.C.P. findings.

Second, functional impairment may be obscured by the large reserve capacity of the exocrine pancreas (Braganza, Hunt & Warwick, 1982).

Third, it seems probable that the secretin-CCK test and E.R.C.P. assess different aspects of the exocrine pancreas and are therefore complementary in the diagnosis of chronic pancreatitis (Oguri, Kasugai et al, 1976; Seligson, Cho et al, 1982). The finding of the present study that the difference between the number of patients with an abnormal test and a normal E.R.C.P. and the number of patients with a normal test and an abnormal E.R.C.P. was not statistically significant, contradicts the opinion that the secretin-CCK test is less sensitive than E.R.C.P. Rather, it supports the view that both modalities are complementary.

The correlations between E.R.C.P. and histological findings will be discussed in III.3

## III.3 THE RELATIONSHIP BETWEEN EXOCRINE FUNCTIONAL IMPAIRMENT AND MORPHOLOGICAL CHANGES IN CHRONIC PANCREATITIS.

One of the unexplored fields in the study of chronic pancreatitis is the relationship between structural and functional changes (Vennes, 1982). As the secretin-CCK test is the most accurate way to measure the exocrine pancreatic function in clinical practice, it seemed worthwile to compare the data of this test with the morphological information obtained in our patients by E.R.C.P and histological examination.

Comparison of individual secretin-CCK test parameters with E.R.C.P. items demonstrated statistically significant correlations between chymotrypsin concentration and output and ductular changes in body and tail of the pancreas. These ductular changes were also shown to be a rather sensitive and specific characteristic of chronic pancreatitis (see table II.5.3). It appears therefore that the best parameters of the secretin-CCK test (as selected by discriminant analysis, see II.3.2.4) were significantly correlated with what can be called the best items of E.R.C.P.. This means that both factors are probably influenced by the same process, although not necessarily at the same moment or at the same rate. As there is no pathophysiological relationship between the enzyme secretion and the small ductuli, the findings cannot be explained otherwise.

Comparison of the secretin-CCK test with histology in 25 patients with chronic pancreatitis demonstrated statistically significant correlations between the best parameters of the test (peak bicarbonate output, mean chymotrypsin concentration and the Z-score) and several histological items (acinar atrophy, small duct dilatation and nerve cell proliferation). Here again, the highest correlation was found between two factors that appear to be not pathophysiologically related, i.e. peak bicarbonate output and acinar atrophy. To explain this phenomenon, it may be assumed that the distinction between acinar and ductular microscopical changes is not verygreat. Such an assumption would be supported by the findings of Bockman and coworkers, who have demonstrated a tubular arrangement of the pancreatic acini with continuous relations between acinar and ductular cells (Bockman, Boydston & Parsa, 1983). More likely, however, is the explanation that the best parameter of functional impairment (chymotrypsin concentration) is correlated with what is probably the best item of histological examination, acinar atrophy, both factors being affected by the same disease process.

In the present study an interesting correlation was found between functional impairment and an increase in the number of intrapancreatic nerve cells. Lesions of nerve cells in chronic alcoholism and pancreatitis have been reported by several authors and are thought to be associated with an increased protein content of the pancreatic juice (Payan, Sarles et al, 1972; Sarles, Sahel et al, 1976; Sarles, Sahel et al, 1980). It is difficult to exclude with certainty that the increase was only apparent because of the loss of acinar tissue, but we found no direct correlation between the degree of atrophy and the increase in nerve cells. In the basal portions of the duodenal contents of alcoholic patients the enzyme concntration was not significantly higher than in nonalcoholic patients.

The fact that no significant correlations could be found between E.R.C.P. data and histological findings in patients with chronic pancreatitis reinforces the existing reservations about the value of E.R.C.P. in the diagnosis of early chronic pancreatitis (Braganza, Hunt & Warwick, 1982; Ruddell, Lintot & Axon, 1983).

These considerations have been summarised in figure III.1.

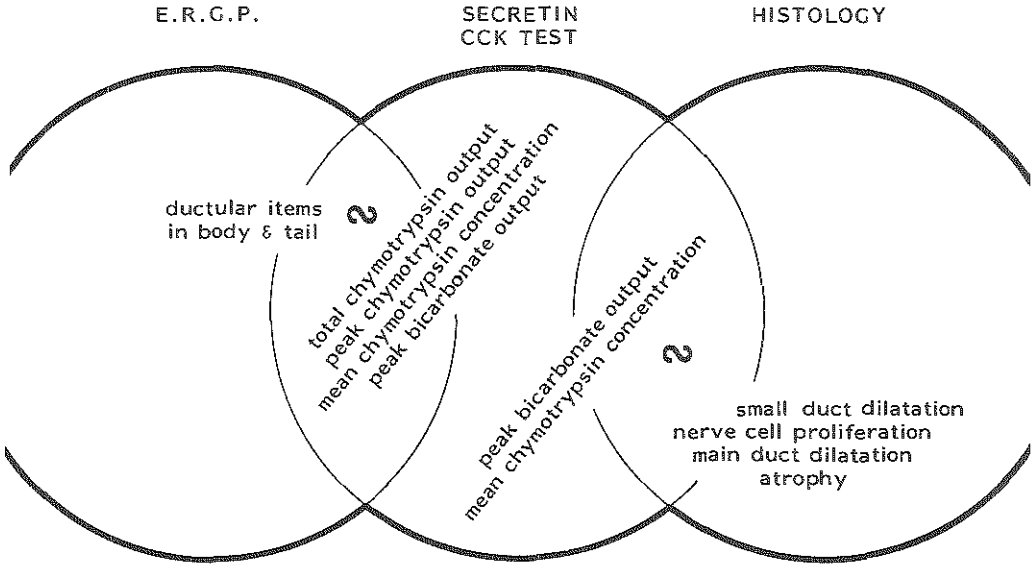



Figure III.1 Schematic representation of relationships between secretin-CCK test, E.R.C.P and histology in chronic pancreatitis.

We conclude that, although statistically significant correlations were found between secretin-CCK test parameters and both E.R.C.P. items and histological changes in chronic pancreatitis, the pathogenetic and pathophysiological relevance of these correlations remains unknown. Elucidation of the relationship between functional and structural changes in chronic pancreatitis will be most difficult to accomplish in the clinical setting: the unacceptability of repeated pancreatic biopsies and E.R.C.P.'s in chronic pancreatitis, and the fact that pancreatic resection specimens are not necessarily representative of the whole gland are but two of the impeding factors.

Therefore, the development of an experimental animal model for chronic pancreatitis appears necessary to elucidate the relationship between structure and function in pancreatic disease.

## III.4 Construction of a diagnostic protocol for nonacute pancreatic disease

With the data obtained in this study an attempt will be made to construct a rational program for the diagnosis of nonacute pancreatic disease. The great majority of the patients with these diseases present with abdominal pain, a small number with jaundice or steatorrhoea. As the analysis of patients with jaundice, whether painless or not, is fundamentally different from the analysis of patients with abdominal pain, they will not be considered separately.

The protocol to be constructed is meant for patients in whom nonacute pancreatic disease, i.e. chronic pancreatitis, pancreatic cancer, painless pancreatic exocrine insufficiency or late complication after acute pancreatitis, is suspected. The first purpose of the diagnostic process is to demonstrate the presence of pancreatic pathology and the second aim is to determine the nature of the disease. In general, pathology of the gastrointestinal and urogenital tract will have been excluded first by the history, physical examination and, where indicated endoscopy, before the suspicion of pancreatic pathology becomes strong enough to warrant analysis. Also, routine laboratory investigations, including liver enzymes, calcium and blood glucose, will have been done already.

A plain film of the upper abdomen, preferably with 50 kV, will be made first because the demonstration of pancreatic calcification indicates the presence of serious pathology that requires further analysis. When the plain film is normal the presence or absence of pancreatic disease will have to be clarified by other means.

Ultrasonography has been advocated in the literature as a screening test for pancreatic disease. The experience in the present study is not in favor of that policy: the low sensitivity and the high failure rate of ultrasonography make this procedure unsuitable as a screening test.

In our opinion, the secretin-CCK test should be performed at this stage of the investigation bacause of its negative predictive value: when the test result is normal, 94% of the patients will not have chronic pancreatic disease. When the test is abnormal, the 70% chance of serious pancreatic pathology justifies further investigation, e.g. computed tomography. The problem is constituted by the 6% of the patients with a normal secretin-CCK test who nevertheless have serious pancreatic disease, occasionally even pancreatic cancer. Estimation of the lactoferrin concentration of duodenal contents and serum pancreatic polypeptide (H.P.P.) estimations may well be able to identify this small group in future.

Computed tomography was performed in a small number of patients in the present series: it showed signs of chronic pancreatitis in 10 out of 11 patients with this disease, signs

of pancreatic cancer in all 3 patients with cancer and various changes in 3 out of 16 patients without chronic pancreatic disease. According to a report in the literature, computed tomography is more accurate than E.R.C.P. in cancer but less accurate in chronic pancreatitis (Foley, Stewart et al, 1980). Computed tomography should probably not be used as a screening test as the diagnostic yield is rather low in that case (Kolmannskog, Vatn et al, 1983). In this series, where this method was applied to patients who had had several other examinations already, no patient with a normal computed tomogram appeared to have chronic pancreatic disease. An advantage of computed tomography is the information about neighbouring structures that is provided. Thus, it may demonstrate irresectability of a tumor. Furthermore, it may be used to guide needle aspiration biopsies of tumors.

Selective angiography of the coeliac and superior mesenteric arteries will be required before pancreatic resection are performed in order to recognise anatomical variations and, in case of a tumor, to exclude vascular ingrowth which means irresectability.

Finally, E.R.C.P. will be seldomly performed in chronic pancreatitis unless surgery is indicated. In that case, an outline of the pancreatic duct may help to plan the type of operation, i.e. resection when the duct is not dilated or drainage when the system is dilated. Visualisation of fistulae and/or pseudocysts may also be important in the planning of surgical procedure. However, E.R.C.P. will not often be required for the decision whether to operate a patient with chronic pancreatitis or not. The role of E.R.C.P. in the diagnosis and management of pancreatic tumors has been limited by the introduction of computed tomography (Freeny & Ball, 1981; Frick, Feinberg & Goodale, 1982).

These considerations have been summarised in an algorithm, figure III.2. Hypotonic duodenography has not been mentioned in this program, because it has no longer a place in the diagnosis of pancreatic disease. Ultrasonography has neither been given a place, not because it has no role, but because it is difficult to determine that role at present. In practice, ultrasonography will often have been performed quite early in the investigation of patients with abdominal pain, e.g. to exclude the presence of gallbladder stones. Similarly, faecal chymotrypsin estimation has been omitted because its low sensitivity makes it unsuitable as a screening procedure.

What will be the benefit of this algorithm, i.e. why not make a computed tomogram of all patients with suspected pancreatic disease?

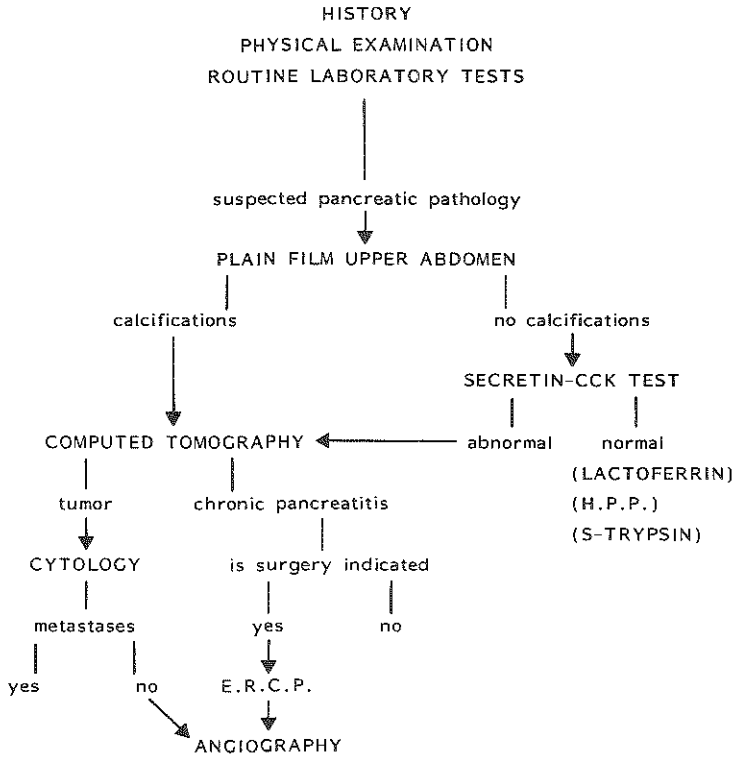
First, computed tomography is not generally available because of its high capital investment and where it is available, waiting lists exist. Thus, selection of patients for

computed tomography reduces the work load and at the same time increases the diagnostic performance of the procedure.

Second, exocrine pancreatic function impairment in chronic pancreatitis is not always coincidental with structural changes. Rather, exocrine function tests appear complementary to imaging procedures like E.R.C.P and computed tomography. Thus, the secretin-CCK test may detect patients that are not demonstrated by the other modalities.

Third, exocrine pancreatic function testing has its specific advantages: it may demonstrate the hitherto seldomly reported painless exocrine pancreatic insufficiency syndrome; it allows the physician to gain insight in the functional capacity of the gland and the need for substitution therapy; finally, it can be of use in the follow up of patients with chronic pancreatitis, for instance to evaluate the effect of alcohol abstinence or of pancreaticojejunostomy on the exocrine function.

Fourth, the cost of the secretin-CCK test is considerably less than that of computed tomography (Hfl 200.- vs Hfl 450.-).




Algorithm for the investigation of suspected pancreatic pathology
Procedures have been printed in CAPITALS
Important aspects of decision making have been written in ordinary print

APPENDIX A DISTRIBUTION OF MEAN AND STANDARD ERRORS OF SECRETIN-CCK TEST PARAMETERS IN EACH GROUP

| Group | 1 | | 2 | | 3 | | 4 | | 6 | | 7 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Size | 25 | | 38 | | 34 | | 10 | | 120 | | 68 | |
| Parameter | Mean | S.E. | Mean | S.E. | Mean | S.E. | Mean | S.E. | Mean | S.E. | Mean | S.E. |
| b.v. | 53.2 | 8.1 | 42.4 | 5.0 | 51.6 | 9.0 | 40.8 | 13.5 | 50.6 | 3.4 | 57.8 | 5.6 |
| b.b.c. | 4.3** | 1.3 | 5.0 | 1.1 | 8.2 | 2.2 | 3.3 | 1.3 | 8.5 | 1.2 | 8.3 | 13.1 |
| b.c.c. | 26.8# | 8.9 | 30.0** | 7.6 | 35.6* | 7.4 | 35.0 | 15.7 | 70.2 | 4.4 | 66.1 | 5.8 |
| p.v. | 135.0* | 13 | 138.9* | 10 | 155.2* | 15 | 100.8# | 10 | 188.4 | 5 | 188.3 | 7 |
| p.b.c. | 52.2# | 6.0 | 61.8# | 6.2 | 63.3# | 5.2 | 61.9# | 9.2 | 90.7 | 2.4 | 94.9 | 2.5 |
| p.b.o. | 5.2# | 0.9 | 7.4# | 1.3 | 8.7# | 1.4 | 4.7# | 0.7 | 14.9 | 0.7 | 14.8 | 0.6 |
| p.c.c. | 43.6# | 7.8 | 50.8# | 6.8 | 63.4# | 11.4 | 63.6# | 16.1 | 99.5 | 3.9 | 100.5 | 4.1 |
| p.c.o. | 5132# | 1233 | 6997# | 1198 | 8139# | 1439 | 5364# | 1702 | 15612 | 641 | 16506 | 827 |
| t.v. | 376.3** | 37 | 377.7** | 27 | 394.4** | 39 | 252.9# | 22 | 513.2 | 16 | 515.3 | 19 |
| m.b.c. | 33.2# | 4.4 | 37.3# | 4.2 | 42.3# | 4.5 | 47.0# | 5.1 | 66.8 | 2.0 | 68.8 | 2.5 |
| t.b.o. | 17.1# | 4.7 | 16.4# | 2.7 | 19.4# | 3.2 | 12.1# | 1.6 | 35.0 | 1.5 | 35.9 | 1.8 |
| m.c.c. | 32.8# | 5.9 | 37.3# | 5.0 | 48.4# | 8.0 | 48.8# | 12.9 | 80.5 | 3.0 | 81.8 | 3.0 |
| t.c.o. | 6155# | 1616 | 7767# | 1362 | 8994# | 1759 | 6002# | 1968 | 17572 | 705 | 18880 | 973 |

Legend: For abbreviation of parameters, see table II.3.1

Levels of significance: * $p<0.05$ ] group 1,2,3 and 4 vs 7
** $0.05<p<0.01$ ]
# $0.01<p<0.001$ ]

underlined values = $p<0.05$: group 1,2 and 3 versus group 4

APPENDIX B DISTRIBUTION OF MEAN AND STANDARD ERRORS OF SECRETIN-CCK TEST PARAMETERS IN EACH ALCOHOLIC AND NONALCOHOLIC SUBGROUP

| Group | 1N | | 1A | | 2N | | 2A | | 3N | | 3A | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Size | 5 | | 20 | | 12 | | 26 | | 20 | | 14 | |
| Parameter | Mean | S.E. | Mean | S.E. | Mean | S.E. | Mean | S.E. | Mean | S.E. | Mean | S.E. |
| b.v. | 37.6 | 12.9 | 56.7 | 10.1 | 33.2 | 8.6 | 46.6 | 6.1 | 47.6 | 13.1 | 57.2 | 12.0 |
| b.b.c. | 2.8 | 2.8 | 5.0 | 1.5 | 6.1 | 1.9 | 4.5 | 1.4 | 9.4 | 3.6 | 6.4 | 1.6 |
| b.c.c. | 24.0 | 9.5 | 29.0 | 11.5 | 21.7 | 7.9 | 33.8 | 10.4 | 31.1 | 9.4 | 42.1 | 12.2 |
| p.v. | 137.4 | 36 | 132.9 | 15 | 122.7 | 13 | 146.4 | 13 | 130.1 | 19 | 190.1* | 20 |
| p.b.c. | 61.9 | 18.0 | 51.6 | 6.2 | 65.6 | 7.7 | 60.1 | 8.4 | 56.8 | 6.9 | 72.6 | 7.7 |
| p.b.o. | 5.9 | 2.8 | 5.3 | 1.0 | 5.9 | 1.3 | 8.1 | 1.8 | 7.0 | 1.8 | 11.1 | 2.0 |
| p.c.c. | 74.0 | 17.3 | 38.0 | 8.3 | 50.8 | 12.1 | 50.8 | 8.5 | 66.7 | 18.4 | 58.8 | 9.5 |
| p.c.o. | 8156 | 3609 | 4606 | 1296 | 5842 | 1610 | 7530 | 1595 | 7439 | 2035 | 9139 | 1998 |
| t.v. | 395.0 | 111 | 369.4 | 40 | 316.1 | 39 | 406.1 | 34 | 314.8 | 46 | 508.2* | 55 |
| m.b.c. | 41.6 | 11.6 | 32.5 | 4.8 | 38.0 | 6.1 | 36.9 | 5.5 | 36.0 | 5.4 | 51.3 | 7.3 |
| t.b.o. | 15.5 | 7.3 | 18.3 | 5.9 | 12.9 | 3.2 | 18.0 | 3.7 | 14.2 | 3.5 | 26.8 | 5.5 |
| m.c.c. | 52.0 | 13.7 | 29.5 | 6.4 | 36.9 | 8.7 | 37.4 | 6.1 | 49.7 | 12.7 | 46.5 | 7.3 |
| t.c.o. | 8916 | 3914 | 5752 | 1858 | 5910 | 1769 | 8625 | 1812 | 7795 | 2453 | 10707 | 2474 |

Legend: For abbreviation of parameters, see table II.3.1

Levels of significance: * $p<0.05$ ] ** $0.05<p<0.01$ ] subgroup A verus N # $0.01<p<0.001$ ]

APPENDIX B DISTRIBUTION OF MEAN AND STANDARD ERRORS OF SECRETIN-CCK TEST PARAMETERS IN EACH ALCOHOLIC AND NONALCOHOLIC SUBGROUP

| Group | 6N | | 6A | | 7N | | 7A | |
|---|---|---|---|---|---|---|---|---|
| Size | 84 | | 36 | | 50 | | 17 | |
| Parameter | Mean | S.E. | Mean | S.E. | Mean | S.E. | Mean | S.E. |
| b.v. | 45.2 | 3.5 | 64.2* | 7.7 | 56.4 | 6.7 | 62.8 | 10.7 |
| b.b.c. | 7.2 | 1.1 | 11.5 | 3.0 | 8.0 | 1.8 | 9.8 | 3.8 |
| b.c.c. | 67.2. | 5.1 | 77.2 | 8.5 | 62.5 | 6.7 | 80.8 | 11.3 |
| p.v. | 182.0 | 6.1 | 204.4 | 11.2 | 188.3 | 7.0 | 188.2 | 18.4 |
| p.b.c. | 94.0 | 2.9 | 81.8* | 4.0 | 94.0 | 2.9 | 96.3 | 4.7 |
| p.b.o. | 15.2 | 0.9 | 14.2 | 1.1 | 14.7 | 0.7 | 14.9 | 1.4 |
| p.c.c. | 100.8 | 4.3 | 96.9 | 8.5 | 101.0 | 4.4 | 104.8 | 9.0 |
| p.c.o. | 15248 | 704 | 16562 | 1395 | 16867 | 1052 | 15144 | 1040 |
| t.v. | 490.1 | 17.0 | 568.6* | 33.8 | 517.1 | 20.2 | 509.4 | 52.5 |
| m.b.c. | 70.0 | 2.3 | 58.6* | 3.9 | 68.1 | 3.1 | 70.1 | 3.8 |
| t.b.o. | 35.2 | 1.8 | 34.5 | 3.0 | 35.4 | 2.1 | 36.8 | 3.9 |
| m.c.c. | 81.1 | 3.3 | 79.3 | 6.6 | 81.9 | 3.7 | 80.4 | 5.1 |
| t.c.o. | 17190 | 805 | 18524 | 1452 | 19184 | 1228 | 17432 | 1273 |

Legend: For abbreviation of parameters, see table II.3.1

Levels of significance: * $p<0.0.5$ ]
** $0.05<p<0.0.1$ ] subgroup A verus N
# $0.01\ p<0.001$ ]

APPENDIX C DISTRIBUTION OF MEAN AND STANDARD ERRORS OF SECRETIN-CCK TEST PARAMETERS IN EACH GROUP PER KG BODY WEIGHT

| Group | 1 | | 2 | | 3 | | 4 | | 6 | | 7 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Size | 23 | | 36 | | 33 | | 10 | | 112 | | 65 | |
| Parameter | Mean | S.E. | Mean | S.E. | Mean | S.E. | Mean | S.E. | Mean | S.E. | Mean | S.E. |
| b.v. | 1.2 | 0.2 | 1.1 | 0.2 | 1.3 | 0.3 | 0.8 | 0.3 | 1.3 | 0.1 | 1.5. | 0.2 |
| b.b.c. | 0.1 | 0.0 | 0.1 | 0.0 | 0.2 | 0.1 | 0.1 | 0.0 | 0.2 | 0.0 | 0.2 | 0.0 |
| b.c.c. | 0.6**0.2 | | 0.8**0.3 | | 0.8**0.2 | | 0.5**0.2 | | 1.8 | 0.1 | 1.7 | 0.2 |
| p.v. | 3.1# | 0.3 | 3.6**0.4 | | 3.8* | 0.4 | 1.8# | 0.3 | 4.7 | 0.2 | 4.8 | 0.3 |
| p.b.c. | 1.3# | 0.2 | 1.6# | 0.2 | 1.5# | 0.2 | 1.1# | 0.2 | 2.3 | 0.1 | 2.5 | 0.1 |
| p.b.o. | 0.1# | 0.0 | 0.2# | 0.0 | 0.2# | 0.0 | 0.1# | 0.0 | 0.4 | 0.0 | 0.4 | 0.0 |
| p.c.c. | 1.1# | 0.2 | 1.3# | 0.2 | 1.6**0.3 | | 1.1# | 0.3 | 2.6 | 0.1 | 2.6 | 0.2 |
| p.c.o. | 121.4# | 28 | 187.2# | 34 | 204.0# | 41 | 94.8# | 33 | 398.3 | 21 | 435.0 | 35 |
| t.v. | 8.8**0.9 | | 9.9**1.0 | | 9.8**1.1 | | 4.6# | 0.6 | 12.9 | 0.6 | 13.4 | 0.7 |
| m.b.c. | 0.8# | 0.1 | 0.9# | 0.1 | 1.0# | 0.1 | 1.0# | 0.1 | 1.7 | 0.1 | 1.8 | 0.1 |
| t.b.o. | 0.5# | 0.2 | 0.4# | 0.1 | 0.5# | 0.1 | 0.2# | 0.0 | 0.9 | 0.1 | 0.9 | 0.1 |
| m.c.c. | 0.8# | 0.1 | 1.0# | 0.1 | 1.2# | 0.2 | 0.8# | 0.2 | 2.0 | 0.1 | 2.1 | 0.2 |
| t.c.o. | 140.9# | 33 | 205.3# | 38 | 232.0# | 51 | 221.5# | 119 | 446.9 | 23 | 501.1 | 41 |

Legend: For abbreviation of parameters, see table II.3.1

Levels of significance: * $p<0.0.5$ ] ** $0.05<p<0.0.1$ ] group 1,2,3 and 4 vs 7 # $0.01<p<0.001$ ]

underlined values = $p<0.05$: group 1,2 and 3 versus group 4

doubly underlined values = $p<0.01$: group 1,2 and 3 versus group 4

APPENDIX D MEAN AND STANDARD ERROR OF FAECAL CHYMOTRYPSIN CONCENTRATION IN EACH GROUP AND SUBGROUP

| (Sub)group | Size | Faecal chymotrypsin concentration in U/g | |
|---|---|---|---|
| | | Mean | Standard Error |
| 1 A+N | 22 | 52.5 | 13.7 |
| 1 A | 18 | 44.0 | 12.7 |
| 1 N | 4 | 91.0 | 50.3 |
| 2 A+N | 35 | 44.4 | 7.6 |
| 2 A | 24 | 33.4 | 7.1 |
| 2 N | 11 | 68.4 | 17.1 |
| 3 A+N | 24 | 64.4 | 15.0 |
| 3 A | 11 | 52.2 | 12.3 |
| 3 N | 13 | 74.8 | 25.9 |
| 4 A+N | 6 | 47.0 | 16.4 |
| 6 A+N | 95 | 90.0 | 6.4 |
| 6 A | 27 | 106.2 | 13.3 |
| 6 N | 68 | 83.5 | 7.2 |
| 7 A+N | 57 | 75.0 | 7.3 |
| 7 A | 13 | 103.0 | 18.6 |
| 7 N | 44 | 66.0 | 7.5 |

| Results Student's t-test: | | | | | |
|---|---|---|---|---|---|
| group | 2 | versus | 7 | p | $<0.01$ |
| subgroup | 1 A | | 7 A | p | $<0.01$ |
| | 2 A | | 7 A | p | $<0.01$ |
| | 3 A | | 7 A | p | $<0.05$ |
| | 7 N | | 7 A | p | $<0.05$ |
| | 1 A | | 6 A | p | $<0.01$ |
| | 2 A | | 6 A | p | $<0.001$ |
| | 3 A | | 6 A | p | $<0.05$ |

SUMMARY

Pancreatic exocrine function, estimated after stimulation with exogenous secretin and cholecystokinin (CCK), is known to be impaired in nonacute pancreatic diseases like chronic pancreatitis and pancreatic cancer. This has been applied to the diagnosis of pancreatic diseases for many years.

Recently, several indirect tests of exocrine pancreatic function have been developed, which have been proposed to provide similar information with less discomfort to the patient. Also in recent years, introduction of a variety of radiological imaging techniques, like endoscopic retrograde cholangiopancreatography (E.R.C.P.), ultrasound and computed tomography have made the pancreas more accessible for diagnostic purposes.

These developments prompted us to reassess the role of the secretin-CCK test in the diagnosis of nonacute pancreatic disease.

In part I of this study an extensive review of the literature on nonacute pancreatic disease and its diagnosis is presented. It appeared that a wide variety of secretin-CCK test procedures exists without, as far as they are comparable, obvious advantages of one method over the other. The method of interpretation of the test data in most studies was found to be not appropriate. Therefore, in this study, discriminant analysis was used for the interpretation of the test data. Furthermore, it was apparent from the literature that not only function tests, whether direct or indirect, but also imaging procedures have their own limitations and advantages. No single procedure has the ideal characteristics that lifts it above all the others.

Thus, the secretin-CCK test did not appear to be outmoded and a reevaluation of its role in the diagnosis of pancreatic disease is indicated.

Finally, it became evident that the relationship between functional impairment and structural or morphological changes, both radiological and histological, in chronic pancreatitis are by and large unknown and unexplored. Thus, it was decided to compare the data of the secretin-CCK test in our patients with those of estimations of faecal chymotrypsin concentration, of E.R.C.P. and of histological examinations.

In part II, the results of the study are presented in 6 chapters. After an outline of the study in chapter II.1, the patient material is presented and discussed in chapter II.2.

The results of the secretin-CCK test and their interpretation by discriminant analysis are given in chapter II.3. The diagnostic performance of the test for chronic pancreatitis was quite satisfactory and comparable to the data

presented in the literature. It appeared also that gastric surgery, unless leading to grossly altered anatomy, does not per se cause abnormal test results. On the other hand, recent acute pancreatitis and a poor general condition may be associated with false abnormal test results.

In chapter II.4 the results of estimation of faecal chymotrypsin concentrations are presented. This estimation appeared not contributing to the diagnosis of nonacute pancreatic disease and its application is therefore not advocated, not even as a screening test.

Correlations between the secretin-CCK test and the E.R.C.P. are reported in chapter II.5. Comparison of individual secretin-CCK test parameters and E.R.C.P. items demonstrated several interesting associations. The overall results of both procedures for the diagnosis of chronic pancreatitis were compatible in 85% of the patients.

Analysis of histological material of 25 patients with chronic pancreatitis and correlation with the data of the secretin-CCK test are presented in chapter II.6. There appeared to be several statistically significant correlations between parameters of the secretin-CCK test and the severity of the histological changes, particularly atrophy and dilatation of the main and small pancreatic ducts. In most cases of chronic pancreatitis an increase in the number of nerve cells was seen that was also correlated with the parameters of the secretin-CCK test.

The general discussion of the results is presented in part III of this study, ultimately yielding an algorithm for the workup of patients with suspected pancreatic disease.

SAMENVATTING

De functie van het exocriene pancreas kan rechtstreeks worden gemeten na stimulatie met exogeen toegediende secretine en cholecystokinine (CCK) en blijkt veelal gestoord te zijn bij niet-acute pancreasziekten zoals chronische pancreatitis en pancreascarcinoom. In de laatste jaren zijn er diverse indirecte pancreasfunctie tests ontwikkeld met de opzet om soortgelijke informatie te verkrijgen als met de secretine-CCK test maar met minder ongemak voor de patient. Bovendien zijn er in de afgelopen jaren een aantal röntgenologische methoden geintroduceerd waarmee een afbeelding van het pancreas kan worden verkregen zoals de endoscopische retrograde cholangio-pancreatografie (E.R.C.P.), de echografie en de computer tomografie. Deze ontwikkelingen op het gebied van de diagnostiek van niet-acute pancreasziekten waren aanleiding tot een poging tot herwaardering van de secretine-CCK test.

In deel I van dit proefschrift wordt een uitgebreid literatuur overzicht geboden betreffende niet-acute pancreatitis en de diagnostische methoden daarvoor. Daaruit bleek onder meer dat er vele verschillende methoden bestaan om de secretine-CCK test uit te voeren. Voorzover deze methoden onderling vergelijkbaar waren, bleken er geen essentiële verschillen tussen te bestaan wat betreft de diagnostische waarde. De wijze van interpretatie van de test gegevens in de meeste publikaties bleek niet te voldoen aan statistische voorwaarden. Daarom werd besloten discriminant analyse te gebruiken voor de verwerking van de eigen gegevens.

Uit de literatuur met betrekking tot de exocriene functie tests, zowel direct als indirect, en de verschillende röntgenonderzoeken bleek dat al deze methoden hun eigen voor- en nadelen hebben en dat geen de procedures duidelijk boven de andere uitsteekt wat betreft diagnostische waarde. Kortom, op grond van de literatuur zijn er geen aanwijzingen dat de secretine-CCK test verouderd is en evaluatie van de test in het licht van de nieuwere diagnostische methoden lijkt dan ook aangewezen.

Tenslotte bleek uit de literatuur dat de relatie tussen exocriene pancreasfunctie stoornissen en morfologische veranderingen, hetzij röntgenologisch dan wel histologisch aangetoond, bij chronische pancreatitis weinig onderzocht en goeddeels onbekend zijn. Daarom werden in dit proefschrift de gegevens van de secretine-CCK test vergeleken met die van de bepaling van het chymotrypsine gehalte in de faeces, van de E.R.C.P. en van het histologisch onderzoek bij patienten met chronische pancreatitis.

De resultaten van het onderzoek zijn gepresenteerd en besproken in deel II van het proefschrift.

In het eerste hoofdstuk (II.1) is de opzet van het onderzoek uiteengezet. In hoofdstuk II.2 worden de patienten gepresenteerd

en besproken.

De secretine-CCK test komt in hoofdstuk II.3 aan de orde. Voor de interpretatie van de test gegevens werd gebruik gemaakt van discriminant analyse. De diagnostische waarde voor chronische pancreatitis bleek tamelijk groot en vergelijkbaar met literatuur gegevens. Bij patienten die maagoperaties hadden ondergaan werd niet vaker een abnormale exocriene pancreasfunctie gevonden dan bij patienten zonder voorafgaande maagchirurgie. Echter, bij patienten met een zodanig veranderde anatomie dat een goede opvang van het duodenumsap niet mogelijk was, bleken de resultaten van de secretine-CCK test niet betrouwbaar. Evenzo bleken bij patienten met een slechte algemene conditie en bij patienten die binnen 6 weken na een aanval van acute pancreatitis werden getest de resultaten niet betrouwbaar te zijn.

In hoofdstuk II.4 werden de resultaten van de bepaling van het chymotrypsinegehalte van de faeces behandeld. Daarbij bleek dat deze bepaling van weinig waarde is voor de diagnostiek van chronische pancreasaandoeningen.

De correlatie tussen de secretine-CCK test en de E.R.C.P. werd in hoofdstuk II.5 besproken. Vergelijking van de individuele secretine-CCK test parameters met de E.R.C.P. criteria leverde een aantal interessante verbanden op. De uitkomsten van beide methodes ten aanzien van de diagnose chronische pancreatitis kwamen bij 85% van de patienten met elkaar overeen.

In hoofdsstuk II.6 werd het histologisch materiaal van 25 patienten met chronische pancreatitis toegelicht en vergeleken met de secretine-CCK test en de E.R.C.P. Er bleken een aantal statistisch significante correlaties te bestaan tussen parameters van de secretine-CCK test en de ernst van de histologische afwijkingen, met name atrofie en dilatatie van de grote en kleine pancreasgangen. Tevens werd een duidelijke toename van het aantal zenuwcellen gevonden bij patienten met chronische pancreatitis, die eveneens was gecorreleerd met de secretine-CCK test parameters.

Tot besluit is in deel III een algemene discussie opgenomen die uitmondt in de opbouw van een beslisboom voor de analyse van patienten die worden verdacht van een niet-acute pancreasziekte.

RÉSUMÉ

Le fonctionnement du pancréas exocrine peut être directement mesuré après activation avec secrétine et cholecystokinine (CCK) et celui-ci semble surtout perturbé chez les maladies pancréatiques non aigues comme la pancréatite chronique et le cancer du pancréas. Ces dernières années différents tests indirects sur le fonctionnementindirect du pancréas ont été développés dans le but d'obtenir des informations analogues à celles du test de secrétine-CCK mais avec moins de désagrément pour le malade. De plus au cours des dernières années un certain nombre de méthodes radiographiques ont été introduites par lesquelles on obtient une image du pancréas comme la wirsungographie endoscopique, l'échographie et le computer tomographie. Ces développements dans le domaine du diagnostic des maladies pancréatiques non aigues ont donné lieu a une recherche sur la valeur du test de secrétine-CCK.

La première partie de cette thèse contient une vaste documentation concernant la pancréatite chronique et les méthodes de diagnostic s'y rapportant. Il en ressort qu'il existe bien de méthodes différentes pour pratiquer le test de secrétine-CCK. Dans la mesure où ces méthodes sont comparable entre elles, il semble qu'il n'existe pas de différences essentiellles en ce qui concerne la valeur du diagnostic. Dans la plupart des publications, la méthode d'interprétation des données du test ne semble pas satisfaire aux conditions statistiques. C'est pour cette raison qu'il a été décidé d'utiliser une analyse discriminante dans l'application des notres données.

Dans les revues se rapportant aux tests directs et indirects de fonctionnement exocrine et aux différent examens radiographique il ressort que ces méthodes ont leur propre avantage et inconvénient et qu'aucun de ces procédés ne surpasse clairement les autres en ce qui concerne sa valeur diagnostique.

En un mot, les publications ne donnent aucune indication qui permettrait de dire que le test de secrétine-CCK est dépassé et la reévaluation du test à la lumière des méthodes diagnostques plus nouvelle semble indiqué.

Enfin, il reste à conclure, d'après ces articles, que la relation entre les troubles de fonctionnement du pancréas exocrine et les changements morphologiques, soit décelés par radiologie ou bien par histologie, a donné lieu jusque là à très peu de recherches pour ce qui est de la pancréatite chronique. C'est pour cette raison que dans cette thèse les données du test de secrétine-CCK sont comparées à celles de l'estimation du taux fécal de chymotrypsin, à celles de la wirsungographie endoscopique et a celles de l'examen histologique du pancréas chez les malades atteints de pancréatite chronique.

Les résultats de cette recherche sont présentés et discutés dans la deuxième partie de la thèse.

Dans le premier châpitre (II.1) le cadre de la recherche est développée. Dans le châpitre (II.2) les malades sont présentés et discutés.

Le test de secrétine-CCK, interprété par l'analyse discriminante, est commentée dans le châpitre II.3. La valeur diagnostique pour la pancréatite chronique semble être assez importante et comparable aux données des revues consultées. Chez les malades ayant subi des opérations d'estomac il n'a pas été observé plus souvent de fonctionnement pancréatique exocrine anormal que chez les malades sans intervention chirurgical d'estomac. Cependant chez les malades ayant subi tel changement anatomique qui ne permettait plus une bonne réception du suc pancréatique les résultats du test secrétine-CCK ne semblent pas être fiables.

Au châpitre II.4 sont étudiés les résultats de l'évaluation du taux fécal de chymotrypsin. Par là il semble que cette estimation ait peu d'importance pour le diagnostic des affections chronique du pancréas.

La corrélation entre le test de secrétine-CCK et la wirsungographie est discutée dans le châpitre II.5. La comparaison des paramètres individuels du test de secrétine-CCK aux critères de wirsungographie pose un certain nombre de relations intéressantes. Les résultats des deux méthodes par rapport au diagnostic de la pancréatite chronique s'accordaient dans 85% des cas.

Dans la châpitre II.6 les matériaux histologiques de 25 malades atteints de pancréatite chronique ont été commentés et comparés aux tests de secrétine-CCK et de wirsungographie. Il en ressort qu'il existe des corrélations essentielles au point de vue statistique entre les paramètres du test S-CCK et la gravité des anomalies histologiques comme l'atrophie ou la dilatation du canaux principaux et secondaires du pancréas. En même temps on a trouvé une augmentation des cellules nerveuses chez les malades atteints de pancréatite chronique qui sont en corrélation avec les paramètres du test de secrétine-CCK.

Pour conclure on trouve dans la troisième parti une discussion générale qui débouche sur l'élaboration des facteurs décisifs nécessaires à l'analyse des malades supposés être atteints d'une maladies non aigues du pancréas.

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