Human pancreatic exocrine response to nutrients in health and disease

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1.0 INTRODUCTION
Optimal digestion and absorption of nutrients requires a complex interaction among motor and secretory functions of the gastrointestinal tract. Digestion of macronutrients is a prerequisite for absorption and occurs mostly via enzymatic hydrolysis. In this context, pancreatic enzymes, in particular lipase, amylase, trypsin, and chymotrypsin, play the most important role but several brush border enzymes as well as other pancreatic and extrapancreatic enzymes also participate in macronutrient digestion. The crucial importance of pancreatic exocrine function is reflected by the detrimental malabsorption in patients with untreated pancreatic exocrine insufficiency, which is a typical complication of, for example, chronic pancreatitis.1–4

Comprehensive knowledge about the physiological pancreatic exocrine response to normal diets and to individual food components and about alterations in pancreatic exocrine insufficiency is necessary to administer a pancreatic enzyme preparation which imitates physiological conditions closely. Although many efforts have been made to substitute for pancreatic exocrine insufficiency by specially designed pancreatic enzyme preparations, these still have several disadvantages compared with physiological enzyme secretion. In particular lipid absorption is not completely normalised in most patients.5

As a basis for a better understanding of pancreatic exocrine function in health and disease this review will first summarise literature data on pancreatic exocrine response to a normal diet and to administration of individual food components in healthy humans. The next chapter will focus on pancreatic responses to a normal diet and to administration of individual food components in patients with pancreatic diseases, in particular chronic pancreatitis, but also in patients with other pancreatic and non-pancreatic diseases which are associated with intraluminal lack of pancreatic enzymes, for instance coeliac disease and diabetes mellitus. Other evidence of pancreatic involvement and dysfunction in these diseases will also be discussed, particularly if sufficient data on endogenously stimulated pancreatic secretion are lacking.

2.0 SECRETORY RESPONSE OF THE EXOCRINE PANCREAS TO NUTRIENTS IN HEALTHY HUMANS

2.1 Introduction
The healthy human pancreas adopts exocrine secretion to nutrient ingestion and there are numerous studies investigating pancreatic exocrine response to various endogenous stimuli. This chapter will summarise literature data on pancreatic exocrine response to a normal diet, its physical and biochemical properties, and to administration of individual food components in healthy humans with respect to total pancreatic secretion, secretion of individual enzymes, ratios of enzymes, intraluminal pH and bicarbonate and bile acid secretion.

2.2 Pancreatic response to a normal diet
In the fasting state, human pancreatic exocrine secretion is cyclical and closely correlated with upper gastrointestinal motility (fig 1).6–8

Ingestion of a regular meal disrupts this interdigestive pattern within a few minutes and induces postprandial enzyme secretion instead, which has also been shown to follow a consistent pattern: enzyme delivery into the duodenum increases rapidly and reaches maximal values within the first postprandial hour,9–10 or even within 20–30 minutes postprandially.11–13 Following peak output, enzyme secretion decreases to a fairly stable secretory rate before decreasing again after about 3–4 hours postprandially to finally reach the interdigestive range at the end of the digestive period (fig 2).13–19 The degree and the duration of the digestive enzyme response are determined by the caloric content,13–14 nutrient composition, and physical properties of the meal.

In addition, the route or site of administration of nutrients strongly influences pancreatic enzyme responses: oral and duodenal application of a complex formula initiate similar increases in secretion of amylase, lipase, and trypsin.15 In contrast, jejunal infusion of nutrients has lower stimulatory potency than duodenal (about 25%)16 while ileal nutrient perfusion inhibits enzyme secretion (compare 2.2.9).17–20 Moreover, intraduodenal administration of an elemental formula equicaloric with the complex formula halved the stimulation of enzyme secretion.15

2.2.1 Influence of the caloric content
Duodenal nutrient exposure is the dominant stimulatory mechanism for the postprandial enzyme response. In order to permanently

Abbreviations: CCK, cholecystokinin; CFTR, cystic fibrosis transmembrane regulator; DPPHR, duodenum preserving pancreatic head resection; ERCP, endoscopic retrograde cholangiopancreatography; GIP, glucagon-like peptide-1; IDDM, insulin dependent diabetes mellitus; MMC, migrating motor complex; NIDDM, non-insulin dependent diabetes mellitus; PPPD, pylorus preserving pancreaticoduodenectomy.

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stimulate pancreatic enzyme secretion and to convert the interdigestive secretory pattern to the fed pattern in response to a mixed meal, intraduodenal nutrient loads of about 1 kcal/min are required. Thus, the cyclical interdigestive pattern was clearly preserved with duodenal nutrient loads of 0.36 kcal/min, independently of whether proteins, carbohydrates, or lipids were perfused.13 However, a recent study has shown that even higher duodenal nutrient delivery rates (1.5–2.67 kcal/min) did not completely abolish cycles of enzyme secretion but modulated cycles by increasing the nadir instead.22 Duodenal perfusion rates in the latter study were chosen to imitate physiological gastric emptying rates of 2–3 kcal/min following ingestion of a normal meal in healthy humans.21 With meals ranging from about 200–500 kcal, a positive correlation between postprandial amylase secretion and meal energy density was observed as a result of initially higher and also longer lasting output of amylase after high energy meals.13 By contrast, when healthy subjects ingested three meals per day containing either 20, 30, or 40 kcal/kg, maximal enzyme response was already achieved by the 20 kcal/kg diet14 (which means 1500 kcal per day or 500 kcal/day containing either 20, 30, or 40 kcal/kg). Maximal enzyme response was already achieved by the 20 kcal/kg diet14 (which means 1500 kcal per day or 500 kcal per meal in a subject with 75 kg bodyweight). Therefore, meals containing about 500 kcal seem to be sufficient to induce maximal enzyme response. However, there is a positive correlation between the duration of digestive secretion and nutrient content also with high caloric meals,14 because digestive pancreatic response is maintained as long as nutrients are emptied at stimulatory rates from the stomach into the duodenum.

2.2.2 Influence of nutrient composition
Chronic ingestion of a high fat diet is associated with higher enzyme outputs than a carbohydrate rich diet (fig 3).24 Following ingestion of a diet low in carbohydrate content (10%) and high in fat content (40%) for four weeks, interdigestive pancreatic enzyme output was about four times higher compared with a high carbohydrate (80%), low fat (10%) diet. Moreover, digestive response to the high fat diet was about twice as high as to the high carbohydrate diet. Diets with more physiological nutrient composition (50% carbohydrate, 10–40% fat, 10–40% protein) had intermediary effects. These alterations were not explained by different caloric content of the meals because caloric content of all diets was adjusted to body weight (at least 30 calories per kg) and usual daily activity (+20%). In contrast to chronic modifications of the diet, acute changes (maintaining or altering diets for 24 hours) did not alter interdigestive enzyme output, but adaptation of postprandial pancreatic enzyme secretion occurred.24

2.2.3 Influence of physical properties
Apart from caloric content and nutrient composition, physical properties of a meal also affect pancreatic secretion. Enzyme response to a solid meal is more sustained compared with an identical meal which has been homogenised.8 This is partly due to slower gastric emptying of the solid compared with the homogenised meal which leads to prolonged stimulation of enzyme output. In addition, increased gastric acid secretion and, consequently, increased duodenal acid delivery in response to a solid meal may also cause a higher pancreatic secretory response.6

Due to better applicability in intubation studies many investigators have used semiliquid, homogenised meals and have shown an overall similar pattern for postprandial pancreatic enzyme secretion compared with solid meals with maximal secretory rates early postprandially, lower, yet stable or slowly declining secretion for about 2–3 hours followed by a fast decrease into the interdigestive range.18 25–27 Other physical properties of a meal such as volume, osmolality, and temperature may also influence pancreatic enzyme secretion, either directly or by altering gastric emptying. Dooley et al report a stepwise increase in pancreatic amylase and bicarbonate secretion in response to duodenal perfusion with increasing flow rates of saline (0.2 to 3.2 ml/min). Increasing osmolality of a duodenally perfused mannitol solution from 370 mosmol/kg to 520 mosmol/kg.

Figure 1 Interdigestive amylase output in healthy volunteers during daytime. Enzyme output is cyclical: it is associated with intestinal motility and is higher during phases II and III compared with phase I (*p<0.05 v phase I).22

Figure 2 Digestive pancreatic enzyme response to a regular meal. Enzyme delivery into the duodenum increases rapidly and reaches maximal values within the first postprandial hour or even within 20–30 minutes postprandially. Following peak output, enzyme secretion decreases to almost stable secretory rates at lower levels until about 3–4 hours postprandially depending on the size of the meal. The interdigestive range is reached again at the end of the digestive period.2,13

Figure 3 Effect of chronic ingestion of diets with varying nutrient composition in healthy volunteers. Following ingestion of a diet low in carbohydrate content (10%) and high in fat content (40%) for four weeks, postprandial enzyme output was about twice as high as following a high carbohydrate (80%), low fat (10%) diet (geometric means, ANOVA: *p<0.05). Interdigestive pancreatic enzyme output was about four times higher with the low carbohydrate, high fat diet. Thus, chronic ingestion of a high fat diet is associated with higher enzyme outputs than a carbohydrate rich diet.28
also increased enzyme secretion, but no further increase was seen with higher osmolality.\textsuperscript{26} The authors conclude that the human duodenum contains receptors for volume (or distension) and osmolality that stimulate pancreatic enzyme and bicarbonate secretion. By contrast, Holtmann \textit{et al} report a close yet inverse correlation between the osmolality of duodenally perfused nutrient solutions within a much lower range (24–290 mosmol/kg) and enzyme secretion. Whether and why there may be differential responses of human pancreatic exocrine secretion to hypo-and iso-osmotic duodenal chyme on the one hand and hyperosmotic chyme on the other hand still needs to be established. It appears that gastric emptying—which is one major regulator of pancreatic exocrine secretion—is not affected by osmolality of ingested liquids in the range 200–400 mosmol/kg.\textsuperscript{29} By contrast, gastric emptying was found to be delayed in some\textsuperscript{10}–\textsuperscript{11} but not all\textsuperscript{12} studies when meal temperature markedly deviated from body temperature. This may indirectly reduce or postpone stimulation of pancreatic exocrine secretion by nutrients entering the duodenal lumen. Direct effects of duodenal chyme temperature on pancreatic secretion may be of less physiological relevance because of the reservoir function of the stomach in which the meal will usually regain body temperature before being emptied.

\subsection{2.2.4 Influence of age and gender}

Whether pancreatic secretion is gender related and decreases in the elderly is controversial. Tiscornia \textit{et al} showed an increase in amylase and lipase secretion in men aged over 45 years and a decrease in flow and bicarbonate output in women of the same age but no differences among younger men and women.\textsuperscript{31} Laugier \textit{et al} reported a slight decrease in bicarbonate and enzyme secretion after the third decade, but even in subjects older than 80 years a less than 20–30\% decrease in secretion was expected, which is far from being clinically significant.\textsuperscript{34} Other authors observed no reduction\textsuperscript{13} or a more marked reduction of pancreatic exocrine function (by about 45\%),\textsuperscript{36} particularly of bicarbonate secretion\textsuperscript{32} in elderly people. Gaia \textit{et al} showed that fluid secretion, bicarbonate, and enzyme output were about 20\% higher in men compared with women, but when flow and output values were related to body surface these differences were no longer apparent.\textsuperscript{37} There are no studies available not addressing the influence of female sexual hormones or different stages of the menstrual cycle on pancreatic exocrine secretion. Furthermore, the influence of age and gender on pancreatic secretion have only been tested by exogenous stimulation.\textsuperscript{33}–\textsuperscript{35} Therefore it remains unclear whether they are of relevance postprandially.

\subsection{2.2.5 Total pancreatic secretion}

Because of interference with meal proteins, duodenal protein output cannot be used as a measure of total pancreatic enzyme secretion following ingestion of regular meals. To overcome this problem some authors added outputs of individual enzymes in order to estimate total pancreatic secretion. Following ingestion of a defined diet for four weeks (10 or 25\% protein, 40 or 25\% fat, 50\% carbohydrates), combined amylase, lipase, and trypsin output was about 90 U/min\textsuperscript{2} kg interdigestively and 210–250 U/min\textsuperscript{2} kg postprandially.\textsuperscript{40} On the other hand, the problem of interference between meal and endogenous proteins can be circumvented by application of a meal without protein component. Under these conditions duodenal protein delivery is totally derived from endogenous sources and mainly from pancreatic enzymes. Following a pure carbohydrate meal containing 50 g rice starch, duodenal protein concentration during the eight hours postprandial period was 5.9 mg/ml and cumulative postprandial duodenal protein delivery 4.6 g. Maximal duodenal protein delivery was achieved one hour postprandially and reached 30 mg/min.\textsuperscript{39} However, this meal is likely to be a submaximal stimulant of pancreatic exocrine secretion.

\subsection{2.2.6 Secretion of individual enzymes}

In physiological studies measuring pancreatic enzyme response to solid or homogenised meals with normal nutrient composition and a caloric content of 300 to about 600 kcal, trypsin and lipase activities were analysed most frequently, amylase was also measured in several studies, but there is little information on chymotrypsin output. Such studies were chosen as the basis for analysis of literature data on digestive enzyme outputs and intraluminal enzyme activities. Enzymatic activities were directly measured in intestinal chyme. Enzyme outputs (or flow rates), on the other hand, were calculated from intraduodenal volume flow and enzyme activities (volume flow \times enzyme activity for a given interval). In order to facilitate comparison of data from different studies, enzyme activities and outputs have been transferred to U/ml and U/min, respectively. However, it has to be kept in mind that varying methods were chosen for measurement of enzyme activities and hardly anybody indicated to have used FIP, Ph Eur, or BP units which impairs comparability of data.

Moreover, the data given below are derived from measurements under optimised assay conditions which are not achieved in vivo. Instead, Carriere \textit{et al} report that in vivo, the specific activities of gastric and pancreatic lipase on meal triglycerides estimated from production of free fatty acids were about two orders of magnitude lower than those measured under optimised assay conditions in vitro.\textsuperscript{48} It is likely that this is also true for amylase and proteases but this has not been investigated.

\subsubsection{2.2.6.1 Intraduodenal enzyme flow rates}

In general, pancreatic enzymes are secreted approximately in parallel. Digestive secretion of all enzymes follows the above described pattern (fig 2) with a short phase of maximal enzyme secretion and a three to sixfold increase above interdigestive levels of lipase,\textsuperscript{49}–\textsuperscript{51} amylase,\textsuperscript{42}–\textsuperscript{45} and trypsin.\textsuperscript{11}–\textsuperscript{15} This is followed by a sustained increase in enzyme output, three to fourfold above preprandial values.\textsuperscript{11}–\textsuperscript{15} In some studies, a more than tenfold stimulation of enzyme secretion even by low caloric meals has been described.\textsuperscript{10}–\textsuperscript{11} This may be due to preferential application of the test meal during phases of low interdigestive enzyme secretion (phase I or early phase II).\textsuperscript{44}

Overall, mean interdigestive pancreatic lipase secretion was about 1000 U/min,\textsuperscript{12} 16 41 45 maximal postprandial enzyme output was about 3000–6000 U/min,\textsuperscript{12} 16 41 and 2000–4000 U/min\textsuperscript{12} 14 41 were stably released into the duodenal lumen for a longer period of time (table 1). Interdigestive amylase output varied from about 50–\textsuperscript{46}–\textsuperscript{48} to 250 U/min.

\textsuperscript{42}–\textsuperscript{45} Postprandially, 500–1000 U/min\textsuperscript{12} 41 45 or even 2000 U/min\textsuperscript{44} were maximally secreted and about 500 U/min were delivered to the duodenum for a longer period of time (table 1).

For trypsin, data are less homogenous, possibly because of methodological differences. In most studies, interdigestive trypsin output ranged from about 50 U/min\textsuperscript{11} 21 42 to 100 U/min.\textsuperscript{10} 12 14 52 53 However, some investigators report a trypsin output of less than 20 U/min\textsuperscript{52} and others about 500–1000 U/min\textsuperscript{54} interdigestively. Accordingly, maximal and sustained postprandial trypsin outputs also vary widely. The majority of investigators report maximal postprandial levels of about 200 U/min\textsuperscript{11} 42 53 to 1000 U/min\textsuperscript{14} 15 100 U/min\textsuperscript{11} 42 53 to about 500 U/min\textsuperscript{21} 51 were stably released into the
duodenum for two hours or longer, depending on the test meal administered (table 1).

2.2.6.2 Duodenal enzyme activities
Most investigators present duodenal enzyme outputs but not direct data if intra-duodenal enzyme activities. These can be calculated if duodenal volume flow rates are given. However, because volume flow is influenced by perfusion rates which vary from about 0 ml/min to 5 ml/min or even 10 ml/min in individual studies, enzyme activities measured in aspirated samples are less comparable than enzyme outputs.

The following data for intraluminal enzyme activities have been derived from studies without marker perfusion or with low marker perfusion rates (3 ml/min or less). In these studies, interdigestive lipase activity ranged from 100 to 400 U/ml. Postprandially, intraluminal lipase activity increased markedly; however, there were minor differences between early and mean postprandial enzyme activities compared with differences between enzyme outputs, and maximal enzyme activities were invariably not reached during the first postprandial hour. This is probably because increased volume flow contributes considerably to the early postprandial output peak.

2.2.7 pH and bicarbonate in vivo (24 h) and in vitro (aspirates)
In duodenal aspirates of healthy subjects, interdigestive pH is 6–7. Following ingestion of a normal meal, duodenal pH is around 6 early postprandially, drops towards 5–5.5 during the second and third postprandial hour, and reaches preprandial values at the end of the digestive period. These data are reported homogenously in all studies investigating pH in aspirates of duodenal chyme. Recent in vivo measurements of intraduodenal pH by 24 hour pH monitoring are generally in line with previous findings, but report slightly lower pH values.

2.2.8 Bile acids
Basal bile acid output (about 10–20 μmol/min) is increased markedly by meal ingestion (three to sixfold). Similar to pancreatic enzyme secretion, peak bile acid output is followed by a period of stable or slowly declining biliary secretion, although the difference between peak and plateau bile acid output tends to be greater than between respective enzyme outputs. Overall, there are fewer data on postprandial bile acid output than expected, because many investigators chose bilirubin output as a measure of biliary secretion. Moreover, in this review only studies with simultaneous measurement of pancreatic and biliary secretion have been taken into account.

2.2.9 Initiation and termination of digestive enzyme response
Sight, smell, and taste of food initiate the cephalic phase of digestive pancreatic enzyme response. Cephalic stimulation is mediated by the vagal cholinergic system and may induce about half-maximal enzyme secretion rates. The subsequent gastric phase accounts for a smaller part of the overall enzyme output and is probably mediated by gastropancreatic reflexes which are activated by gastric distension. The quantitatively most important intestinal phase is induced by the entry of chyme into the duodenum. Gastric acid, free fatty acids, essential amino acids and carbohydrates within the duodenum initiate the intestinal phase of the digestive pancreatic exocrine response and maintain stimulation during the digestive period. Late postprandially, however, pancreatic enzyme output declines to interdigestive values, although the proximal small intestine is still exposed to substantial nutrient concentrations. This is probably not due to inhibitory mechanisms induced by duodenal nutrient exposure—for example, release of somatostatin or pancreatic polypeptide. The liberation of these inhibitory mediators coincides with the release of stimulatory hormones. Therefore, duodenal hormonal inhibitors are generally assumed to be modulators of the magnitude of the digestive response rather than its duration. Another potential mechanism might be desensitisation of pancreatic responsiveness as a result of persistent duodenal nutrient exposure. However, there is no evidence that prolonged duodenal perfusion with constant rates of nutrients decreases pancreatic responsiveness to endogenous stimulation. Therefore inhibitory mechanisms activated predominantly in the late postprandial period are more likely to mediate the termination of digestive pancreatic enzyme secretion in the presence of duodenal nutrient exposure. Candidate hormones are peptide YY (PYY) and glucagon-like peptide-1 (GLP-1). These peptides are released from the distal intestinal mucosa in response to a meal or intraleral nutrients (fig 4). Ideal perfusion of lipids inhibits secretory and motor functions of upper gastrointestinal organs both in the interdigestive state and during weak or moderate endogenous stimulation (fig 5). In addition, there are several studies suggesting comparable inhibitory effects of

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<th>Table 1 Duodenal enzyme outputs</th>
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Data are derived from studies using test meals with 300–600 kcal. References are given in the text.

1. Basal bile acid output (about 10–20 μmol/min) is increased markedly by meal ingestion (three to sixfold).
2. Similar to pancreatic enzyme secretion, peak bile acid output is followed by a period of stable or slowly declining biliary secretion, although the difference between peak and plateau bile acid output tends to be greater than between respective enzyme outputs.
3. Overall, there are fewer data on post-prandial bile acid output than expected, because many investigators chose bilirubin output as a measure of biliary secretion. Moreover, in this review only studies with simultaneous measurement of pancreatic and biliary secretion have been taken into account.
4. The following data for intraluminal enzyme activities have been derived from studies without marker perfusion or with low marker perfusion rates (3 ml/min or less).
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8. Recent in vivo measurements of intraduodenal pH by 24 hour pH monitoring are generally in line with previous findings, but report slightly lower pH values.
9. Similar to pancreatic enzyme secretion, peak bile acid output is followed by a period of stable or slowly declining biliary secretion, although the difference between peak and plateau bile acid output tends to be greater than between respective enzyme outputs. Overall, there are fewer data on post-prandial bile acid output than expected, because many investigators chose bilirubin output as a measure of biliary secretion. Moreover, in this review only studies with simultaneous measurement of pancreatic and biliary secretion have been taken into account.
10. Therefore, duodenal hormonal inhibitors are generally assumed to be modulators of the magnitude of the digestive response rather than its duration. Another potential mechanism might be desensitisation of pancreatic responsiveness as a result of persistent duodenal nutrient exposure. However, there is no evidence that prolonged duodenal perfusion with constant rates of nutrients decreases pancreatic responsiveness to endogenous stimulation.
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12. Ideal perfusion of lipids inhibits secretory and motor functions of upper gastrointestinal organs both in the interdigestive state and during weak or moderate endogenous stimulation.

<table>
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Data are derived from studies using test meals with 300–600 kcal and using no or only low marker perfusion rates (<3 ml/min). References for lipase are given in the text.
equicaloric amounts of carbohydrates, especially glucose (fig 5).17 73 By contrast, perfusion of protein or protein hydrolysates has no17 74 75 or only weak inhibitory effects,70 although the effect on pancreatic enzyme secretion remains largely to be determined. Under physiological circumstances, considerable amounts of nutrients pass the small intestine unabsorbed. This phenomenon is referred to as “physiological malabsorption”. Up to 20% of a carbohydrate meal may reach the terminal ileum17 76 77 and following ingestion of a mixed meal ileal lipid concentrations of up to about 10 mg/ml were measured.57 78 79 There are fewer data on physiological malabsorption of proteins because it has been difficult to differentiate between dietary and endogenous proteins. A recent study using labeled egg protein suggests that about 6% of cooked and 35% of raw egg protein escape digestion and absorption in the small intestine in healthy humans.78

Figure 4 Ileal lipid exposure dose dependently releases glucagon-like peptide-1 (GLP-1) and peptide YY (PYY) in healthy humans.20

Figure 5 Inhibition of endogenously stimulated pancreatic enzyme secretion by ileal perfusion of carbohydrates (CHO) and lipids in healthy humans.17

Decreased thereafter. The resulting relative increase in late postprandial ileal nutrient exposure correlated tightly with the termination of the digestive pancreatic secretory response (fig 6). Therefore, the ileum appears to contribute to the regulation of the transition from the fed to the subsequent fasting state. Stimulatory and inhibitory mechanisms induced by nutrients both in the proximal and distal small bowel may interact to co-regulate pancreatic exocrine secretion during the functional interface between the late postprandial and the subsequent interdigestive period.

2.3 Pancreatic response to protein diets
2.3.1 Enzyme secretion
The protein component of a meal contributes markedly to induction of the digestive pancreatic enzyme response. Overall, mixed amino acids have the same effect on pancreatobiliary secretions compared with polymeric protein solutions.80 However, the stimulatory effect of dietary protein on pancreatic exocrine secretion appears to depend on adequate protein digestion16 and stimulatory potency is limited to certain essential amino acids: phenylalanine, valine, methionine, and tryptophane increased trypsin secretion (300–180% compared with NaCl), whereas isoleucine, leucine, lysine, threonine, and other amino acids did not.81 Even low doses of intraduodenally perfused essential amino acids have a stimulatory effect on pancreatic enzyme secretion. Graded intraduodenal essential amino acid perfusion at 0, 62.5, 125, 225, and 450 μmol/min dose-dependently increased trypsin and chymotrypsin outputs. In these experiments, at least 225 μmol/min were needed to significantly increase protease output above basal levels.82 If only essential amino acids with stimulatory potency were perfused, even 150 μmol/min induced a sustained twofold increase in amylase secretion (53 U/min v 85 U/min).83 Constant intraduodenal perfusion of essential amino acids at a higher dose (800 μmol/min) caused a short lived (<30 min) peak trypsin output (basal: 25 U/min, peak: 160 U/min) followed by a stable 50% maximal enzyme output (about 120 U/min) throughout amino acid perfusion (>5 hours).84

Doubling the protein content of an otherwise unchanged low caloric test meal also doubled cumulative lipase output.85 However it has to be taken into account that these meals had different caloric loads which were within the range of dose-dependent stimulation of enzyme output.13

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Lipids are the strongest stimulants of pancreatic enzyme secretion; thus, administration of a diet with a high fat content for four weeks was associated with higher enzyme concentrations (about 2 mg/ml and 1 mg/ml, respectively) than would be expected after ingestion of a normal meal.16

Nevertheless, ileal nutrient concentration corresponded to up to about 25% of maximal duodenal values and remained stable for almost four hours, whereas duodenal nutrient concentration peaked one hour postprandially, was maintained at increased levels for about two hours and rapidly decreased thereafter. The resulting relative increase in late postprandial ileal nutrient exposure correlated tightly with the termination of the digestive pancreatic secretory response (fig 6). Therefore, the ileum appears to contribute to the regulation of the transition from the fed to the subsequent fasting state. Stimulatory and inhibitory mechanisms induced by nutrients both in the proximal and distal small bowel may interact to co-regulate pancreatic exocrine secretion during the functional interface between the late postprandial and the subsequent interdigestive period.

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The protein component of a meal contributes markedly to induction of the digestive pancreatic enzyme response. Overall, mixed amino acids have the same effect on pancreatobiliary secretions compared with polymeric protein solutions.80 However, the stimulatory effect of dietary protein on pancreatic exocrine secretion appears to depend on adequate protein digestion16 and stimulatory potency is limited to certain essential amino acids: phenylalanine, valine, methionine, and tryptophane increased trypsin secretion (300–180% compared with NaCl), whereas isoleucine, leucine, lysine, threonine, and other amino acids did not.81 Even low doses of intraduodenally perfused essential amino acids have a stimulatory effect on pancreatic enzyme secretion. Graded intraduodenal essential amino acid perfusion at 0, 62.5, 125, 225, and 450 μmol/min dose-dependently increased trypsin and chymotrypsin outputs. In these experiments, at least 225 μmol/min were needed to significantly increase protease output above basal levels.82 If only essential amino acids with stimulatory potency were perfused, even 150 μmol/min induced a sustained twofold increase in amylase secretion (53 U/min v 85 U/min).83 Constant intraduodenal perfusion of essential amino acids at a higher dose (800 μmol/min) caused a short lived (<30 min) peak trypsin output (basal: 25 U/min, peak: 160 U/min) followed by a stable 50% maximal enzyme output (about 120 U/min) throughout amino acid perfusion (>5 hours).84

Doubling the protein content of an otherwise unchanged low caloric test meal also doubled cumulative lipase output.85 However it has to be taken into account that these meals had different caloric loads which were within the range of dose-dependent stimulation of enzyme output.13
output compared with diets rich in carbohydrates or proteins.\textsuperscript{24} Duodenal free fatty acids rather than triglycerides appear to be responsible for the release of cholecystokinin (CCK) and subsequent stimulation of enzyme output in humans.\textsuperscript{34, 41} Duodenal perfusion of fatty acids (oleic acid) at graded doses (0, 50, 100, 200, and 400 \textmu mol/min) dose dependently increased amylase output (0.7, 1.15, 1.24, 1.4, and 1.7 kU/min respectively). Even the lowest dose of 50 \textmu mol/min significantly stimulated enzyme secretion. Overall pancreatic enzyme response paralleled plasma CCK plasma concentrations.\textsuperscript{45}

Apart from the dose of fatty acids delivered to the duodenum, fatty acid chain length has a major influence on pancreatic enzyme response: glycerol did not influence enzyme secretion, increasing fatty acid chain length augmented pancreatic responses.\textsuperscript{34} Accordingly, medium chain triglycerides administered to the proximal jejunum did not increase enzyme secretion in contrast to equicaloric amounts of long chain fatty acids.\textsuperscript{34} Furthermore, the terminal carboxy group of the fat molecule appears to be of importance because oleic acid had a much stronger stimulatory effect on pancreatic secretion than oleyl alcohol.\textsuperscript{40} On the other hand, fat droplet size appears to have no major effect on lipase output: Armand \textit{et al} showed that a lipid emulsion with small droplets (0.7 \textmu m) was digested more efficiently in the upper gastrointestinal tract than a coarse emulsion (10 \textmu m) but gastric and pancreatic lipase activities were similar with both emulsions and overall fat assimilation was unchanged.\textsuperscript{47}

Trypsin output in response to a mixed, fat rich meal (580 kcal, 60% fat) was within the range observed for meals with regular nutrient composition (plateau output: 400–500 U/min).\textsuperscript{32} These findings may imply that within a certain range caloric content plays a major role for determination of pancreatic enzyme response than the proportion of individual nutrient components.

2.4.2 pH and bicarbonate in vivo (24 h) and in vitro (aspirates)
Graded duodenal fatty acid perfusion (0, 50, 100, 200, and 400 \textmu mol/min) dose dependently increased bicarbonate output (13, 17.3, 10.2, 66.9, 92.3 \textmu mol/min respectively (*\textit{p} < 0.05 v 0 \textmu mol/min). However, fatty acids are a weaker stimulant of bicarbonate secretion compared with enzyme secretion. Stimulation started at a dose of 200 \textmu mol/min and paralleled secretin release.\textsuperscript{41} There appear to be no studies measuring duodenal pH in response to lipid meals.

2.4.3 Bile acids
The bile acid response to graded doses of duodenal fatty acids parallels pancreatic enzyme response and CCK release. Infusion of 50, 100, 200, and 400 \textmu mol/min oleic acid significantly and dose dependently increased bile acid output compared with basal levels (85, 70, 89, 99, v 23.5 \textmu mol/min).\textsuperscript{41} The bile acid response to a fat rich liquid meal (580 kcal, 60% fat) paralleled the pancreatic enzyme response, apart from the fact that plateau bile acid output during the second and third postprandial hour was lower than plateau trypsin output in relation to respective peak output rates.\textsuperscript{32}

### 2.5 Pancreatic response to carbohydrate diets

#### 2.5.1 Enzyme secretion
Carbohydrates are weaker stimulants of pancreatic enzyme secretion compared with proteins and lipids.\textsuperscript{1} Most investigators report a marked but short lived increase in enzyme output induced by carbohydrate meals followed by a fast decline.\textsuperscript{41, 43} 100 g glucose dissolved in 500 ml water increased basal lipase output (800 U/min) about threefold (2600 U/min). However, one hour postprandially lipase output had already returned to preprandial values. By contrast, a liquid meal with similar caloric content increased lipase secretion for more than two hours.\textsuperscript{4} On the other hand, test meals containing either 100 g of glucose alone or 100 g of glucose and 35 g of protein, induced similar, though overall submaximal trypsin responses.\textsuperscript{86} Layer \textit{et al} investigated the effect of a pure rice starch meal on protein and enzyme output and on intraluminal protein concentration and enzyme activities. These data are given in Table 3.\textsuperscript{10}

In those studies cited above, liquid monomeric or polymeric carbohydrate solutions were used. Therefore, the lower digestive pancreatic enzyme response to carbohydrate meals may depend in part on faster gastric emptying of the carbohydrate solution compared with either fat containing liquid test meals or solid meals.

#### 2.5.2 Bile acids
Bile acid output was significantly stimulated three to fourfold by 100 g of glucose alone or 100 g of glucose and 35 g of protein.\textsuperscript{24}

### 2.6 Ratios of enzymes

#### 2.6.1 Ratios of pancreatic enzymes
In general, output of pancreatic enzymes into the duodenum occurs in parallel and this becomes evident from most studies which analysed two or more enzymes.\textsuperscript{11, 12, 50} Overall, postprandial lipase:amylase ratio and lipase:trypsin ratio are approximately 3–6/1 and 5–10/1, respectively (compare tables 1 and 2). This means that in terms of catalytic units as defined under optimised conditions in vitro, a three to sixfold excess of lipolytic activity in comparison with amylase and a five to tenfold excess of lipolytic activity in comparison with trypsin is released into the duodenum. It does not automatically imply that the ability of human intestinal contents to digest lipids is higher than the ability to digest proteins or carbohydrates. However, only very few investigators adressed the relations between pancreatic enzymes directly and systematically. Such studies showed that under
experimental conditions—that is, during weak duodenal stimulation and during low dose ileal nutrient perfusion pancreatic amylase seems to be less susceptible to stimulatory and inhibitory mediators, respectively, compared with trypsin and lipase (fig 7). This led to alterations in amylase:protease and amylase:lipase ratios which may occur physiologically at the very beginning and at the end of the digestive period. Although the concept of non-parallel pancreatic enzyme secretion is mostly debated in humans, the group of Morisset has published data showing individual regulation of each pancreatic enzyme under experimental conditions in rats.

In addition, there is evidence that chronic dietary habits may influence enzyme ratios in humans. Intraindividually, the ratio between amylase and lipase is not influenced acutely by the fat content of a meal. By contrast, interindividually there is a correlation between body weight and the amylase:lipase ratio—the heavier the subjects were, the lower this ratio was. Therefore, long time dietary differences might influence enzyme composition with relative dominance of amylase in lighter subjects and of lipase in heavier subjects. Theoretically, high fat diets in heavier subjects might not only cause increased overall enzyme secretion but specifically increase lipase secretion.

2.6.2 Ratios of pancreatic and non-pancreatic digestive enzymes

The ratio between pancreatic and non-pancreatic enzymes changes postprandially. Following infusion of a standard semiliquid test meal (375 kcal) into the stomach, intraduodenal pancreatic lipase activity plateaued at 200 μg/ml (equivalent to 1600 U/ml) until 60% of the meal were emptied from the stomach. Afterwards, pancreatic lipase activity decreased to 50 μg/ml or 400 U/ml. By contrast, gastric lipase activity in duodenal chyme was low during the early postprandial period (about 10 μg/ml) and increased late postprandially (up to 90 μg/ml). Consequently, the ratio between pancreatic and gastric lipase decreased postprandially from 8.4 (wt/wt) during the first postprandial hour to 1.6 during the third hour. Globally, during the whole digestive period, gastric lipase hydrolysed 17.5% of the triglyceride acyl chains (10% intragastrically, 7.5% within the duodenal lumen).

Likewise, salivary amylase occurs as a sharp peak late postprandially in duodenal juice, leading to a marked decrease in the ratio between pancreatic and salivary amylase. Throughout the digestive period, salivary amylase comprises about 15% of total amylase output.

2.7 Fate of enzymes during small intestinal transit

Following ingestion of 50 g pure rice starch (<300 mg fat and protein) only about 8%, 85%, and 64% of lipase, amylase, and trypsin, respectively, reached the mid-jejunum, whereas 1%, 74%, and 22% of lipase, amylase, and trypsin respectively, reached the terminal ileum (table 3). This means that lipase activity is almost completely lost during small intestinal transit in the absence of its substrate. Compared with lipase activity, lipase immunoreactivity was preserved significantly longer. Vice versa, trypsin activity survived small intestinal transit better than trypsin immunoreactivity. Consequently, complete structural integrity of the molecule may not be essential for its proteolytic activity.

Following ingestion of a mixed meal or duodenal perfusion of graded doses of mixed nutrients similar amounts of amylase reached the terminal ileum, whereas considerably higher amounts of lipase (20–25% of duodenal lipase) survived small intestinal transit. In vitro and in vivo survival of pancreatic enzymes is enhanced by the presence of nutrients, in particular of the respective substrate. Proteases, especially chymotrypsin, play a major role in the destruction of lipolytic activity during aboral small intestinal transit. Interestingly, the protective effect of nutrients on degradation of lipase was as high as the effect of protease inhibition.

2.8 Summary

Current knowledge about the physiological pancreatic exocrine response to a meal can be summarised as follows:

Pattern and magnitude of digestive pancreatic enzyme response have been described consistently by several authors. In response to an ordinary meal or application of individual nutrients, there is a short phase of maximal enzyme secretion which means a three to sixfold increase above interdigestive levels of all major enzymes. This is followed by a three to fourfold sustained increase in enzyme output. Secretory rates return to the interdigestive range late postprandially (see 2.2).

The degree and the duration of the digestive enzyme response are determined by the caloric content, nutrient composition, and physical properties of the meal: Meals containing about 500 kcal appear to be sufficient to induce the maximal enzyme response (see 2.2.1). Lipids are the strongest stimulants of pancreatic enzyme secretion and chronic administration of a diet with a high fat content is permanently associated with higher enzyme output compared with diets rich in carbohydrates or proteins. Duodenal free fatty acids rather than triglycerides appear to be responsible for the release of CCK and subsequent stimulation of enzyme output in humans. The stimulatory potency of proteins is limited to the essential amino acids phenylalanine, valine, methionine, and tryptophane. Carbohydrates are weaker stimulants than lipids and proteins. Maximal postprandial enzyme output to carbohydrate solutions is comparable to lipid and protein diets tested in various studies, however, the latter cause a more sustained increase in enzyme output. The relevance of faster gastric emptying of liquid and semiliquid carbohydrate meals has not been clarified, so far. This would require circumventing gastric emptying by duodenal perfusion of individual nutrient solutions (for example, equicaloric and/or same molar concentrations of fatty acids, essential amino acids with stimulatory potency and glucose) (see 2.2.2 and 2.3–2.5).

Enzyme response to a solid meal is more sustained compared with an identical meal which has been homogenised. This is partly due to slower gastric emptying of the solid compared with the homogenised meal which leads to prolonged stimulation of enzyme output. In addition, increased gastric acid secretion and, consequently, increased...
duodenal acid delivery in response to a solid meal may also cause higher pancreatic secretory response. The effects of other physical properties of a meal, such as osmolality and temperature, have so far not been clarified (see 2.2.3).

It is controversial whether pancreatic secretion is gender related and decreases in the elderly. In any case, differences in pancreatic exocrine secretion among women and men on the one hand and young and elderly adults on the other hand are probably small and clinically unimportant. The influence of female sexual hormones or different stages of the menstrual cycle on pancreatic exocrine secretion have not been investigated, so far (see 2.2.4).

There are only a few studies addressing total digestive pancreatic enzyme output. It can be estimated by duodenal protein delivery if the test meal does not contain proteins because under these circumstances duodenal proteins are totally derived from endogenous sources and mainly from pancreatic enzymes. Following submaximal digestive stimulation by a pure rice starch meal, duodenal protein concentration during the postprandial period is about 6 mg/ml and cumulative postprandial duodenal protein delivery 4.6 g. Maximal duodenal protein delivery is achieved one hour postprandially and reaches 30 mg/min (see 2.2.5).

In physiological studies, individual digestive enzymes have been analysed more frequently, in particular trypsin and lipase. Amylase was also measured in several studies, but there is astonishingly little information on chymotrypsin output. Duodenal enzyme outputs (see table 1) are easier to compare among the different studies than intraluminal enzyme activities (see table 2), because the latter are more profoundly influenced by methodological differences, particularly by marker perfusion. Overall, mean interdigestive pancreatic lipase, amylase, and trypsin outputs are about 1000, 50–250, and 50–100 U/min, respectively. Maximal postprandial outputs reach about 3000 to 6000 U/min for lipase, 500–1000 U/min for amylase, and 200–1000 U/min for trypsin. Thereafter, 2000–4000 U/min of lipase, 500 U/min of amylase, and 150–500 U/min of trypsin are stably released into the duodenum for two hours or longer, depending on the test meal administered (see 2.2.6).

Nutrients within the duodenal lumen are the most important stimulators of the pancreatic exocrine response and maintain enzyme secretion throughout the digestive period. However, the distal small intestine also participates in the regulation of the pancreatic response to a meal. Late postprandially, stimulatory and inhibitory mechanisms induced by nutrients both in the proximal and distal small bowel seem to interact to co-regulate pancreatic exocrine secretion during the functional interface between the late postprandial and the subsequent interdigestive period (see 2.2.9).

In general, output of pancreatic enzymes into the duodenum occurs in parallel and this becomes evident from most studies which analysed two or more enzymes. Postprandial lipase:amylase ratio and lipase:trypsin ratio are approximately 3–6/1 and 5–10/1, respectively (see tables 1 and 2). However, there appear to be no studies addressing this question directly and systematically. Moreover, under experimental conditions—that is, during weak duodenal stimulation and during low dose ileal nutrient perfusion, pancreatic amylase seems to be less susceptible to stimulatory and inhibitory mediators, respectively, compared with trypsin and lipase. This leads to alterations in amylase:protease and amylase:lipase ratio which may occur physiologically at the very beginning and at the end of the digestive period (see 2.6).

Postprandially, the ratio between pancreatic and non-pancreatic enzymes in duodenal juice changes markedly. The ratio between pancreatic and gastric lipase decreases from 8.4 (wt/wt) during the first postprandial hour to 1.6 during the third hour. Likewise, salivary amylase occurs as a sharp peak late postprandially in duodenal juice, leading to a marked decrease in the ratio between pancreatic and salivary amylase (see 2.6).

During small intestinal transit, lipase activity is most susceptible to destruction and is almost completely lost following a carbohydrate meal. If subjects ingest a mixed meal and following duodenal perfusion of mixed nutrient solutions, significantly higher amounts—that is, about 20% of duodenal lipase reach the terminal ileum in active form (see 2.7).

3.0 PATHOPHYSIOLOGY OF PancreATIC EXOCRINE SECRETION

The crucial importance of pancreatic exocrine function is reflected by the detrimental malabsorption which occurs as a consequence of untreated pancreatic exocrine insufficiency and may be due to different diseases.\(^8\)\(^9\)\(^{10}\) In chronic pancreatitis, which is the most common cause of pancreatic exocrine insufficiency, intraluminal availability of pancreatic enzymes decreases because of destruction of functioning pancreatic parenchyma causing insufficient amounts of enzymes to be synthesised and secreted into the duodenum in response to ingestion of a meal. Other, virtually pancreatic causes of intraluminal enzyme deficiency include: cystic fibrosis, pancreatic resections, and pancreatic carcinoma. However, even in the absence of (primary) pancreatic disease, there are other pathophysiological mechanisms which may also cause intraluminal lack of enzymatic activity and malabsorption. Periampullary tumours, for instance, may obstruct the main pancreatic duct and impair secretion of pancreatic juice despite normal synthetic capacity. In coeliac sprue, on the other hand, reduced endogenous stimulation is the main cause of decreased pancreatic exocrine secretion. Patients with Zollinger-Ellison syndrome may suffer from malabsorption due to intraluminal inactivation of enzymes, particularly lipase, caused by duodenal hyperacidity. Gastrointestinal surgery—for example, gastrectomy and Roux-en-Y anastomosis—may impair coordination between secretory and motor functions and thereby induce malabsorption and malabsorption (fig 8).\(^9\)\(^7\)\(^{10}\)\(^{11}\)

Further understanding of the pathophysiological mechanisms is needed for optimising enzyme replacement therapies, because in most patients luminal lipid digestion cannot be completely normalised by currently available enzyme preparations.\(^{10}\)\(^2\)\(^{10}\)\(^3\) Moreover, it has to be taken into account that in states of chronic intraluminal enzyme deficiency, complex and interacting alterations of secretory, motor, and endocrine functions may contribute to symptoms which may even precede overt malabsorption.\(^1\)\(^{10}\)

This chapter will focus on pancreatic responses to a normal diet and to administration of individual food components in patients with pancreatic diseases (that is, acute and chronic pancreatitis, pancreatic cancer, pancreatic surgery, and cystic fibrosis) as well as non-pancreatic diseases associated with intraluminal lack of pancreatic enzymes (that is, coeliac disease, diabetes mellitus, Crohn's disease, gastric surgery, short bowel syndrome, and Zollinger-Ellison syndrome). Other evidence of pancreatic involvement and dysfunction in these diseases—for example, pancreatic response to exogenous stimulation—will also be discussed, in particular if sufficient data on endogenously stimulated pancreatic secretion are lacking. On the other hand, the influence on other organs apart from the pancreas by the diseases under discussion will only be reviewed if they influence pancreatic function or the degree of dysfunction tolerated without nutrient malabsorption and malabsorption.
3.1 Chronic pancreatitis

Chronic pancreatitis is the most common cause of pancreatic exocrine insufficiency. Although pancreatic exocrine function may already decrease during the early stages of the disease because of loss of functioning parenchyma, overt malabsorption is a late complication in most patients because of the large reserve capacity of the exocrine pancreas. It is widely accepted that steatorrhoea and creatorrhoea do not occur until secretion of the respective digestive enzymes is decreased below 5–10% of normal.

In consequence, patients with suspected chronic pancreatitis may show a broad spectrum of pancreatic function ranging from normal enzyme output to “compensated” (mild to moderate) exocrine insufficiency—that is, enzyme output less than normal but sufficient to prevent nutrient malabsorption and “decompensated” (severe) exocrine insufficiency with clinical steatorrhoea.

The fact that patients with variable degrees of pancreatic exocrine insufficiency have been investigated is probably one of the main reasons for variable findings in studies on pancreatic enzyme function in chronic pancreatitis showing approximately a 40–90% or even 99% reduction of enzyme release compared with healthy humans (table 4). On the other hand, in most studies patients with varying aetiologies of chronic pancreatitis, for example alcoholic and idiopathic, have been included. The different natural courses of chronic pancreatitis suggest that pancreatic exocrine function is preserved longer and consequently exocrine insufficiency may generally be milder in “early onset” idiopathic chronic pancreatitis compared with alcoholic and “late onset” idiopathic chronic pancreatitis. However, direct comparisons of enzyme and bicarbonate outputs in patients with varying aetiologies of chronic pancreatitis have hardly been performed, so far. For alcoholic and tropical chronic pancreatitis, Sarles et al demonstrated that both show similar biochemical modifications of pancreatic juice including protein output.

3.2.2 Pancreatic response to mixed meals

DiMagno et al investigated pancreatic enzyme output in response to a mixed meal in patients with chronic pancreatitis, steatorrhoea, and creatorrhoea—that is, severe pancreatic exocrine insufficiency. In chronic pancreatitis patients, digestive lipase output was about 2.5 IU/min which was less than 0.2% of normal (3000 IU/min). Oral pancreatin (eight times 3.5 kU of lipase per meal) increased duodenal lipase to reach about 1% of normal which is obviously still far below the minimum of 5 to 10% of normal needed to prevent steatorrhoea. Similarly, Layer et al investigated digestive responses to a 300 kcal semiliquid meal in patients with severe pancreatic exocrine insufficiency (that is, SC test results <5% of normal) in comparison to healthy volunteers. Oro-ileal intubation and aspiration of aliquots of chyme further allowed estimation of intestinal nutrient absorption. Severe exocrine insufficiency was associated with considerable maldigestion and malabsorption: in chronic pancreatitis patients, about 40% of nutrients (487 kJ of 1257 kJ) were delivered to the terminal ileum compared with about 5% of nutrients (69 kJ) which were physiologically malabsorbed in healthy humans. In these chronic pancreatitis patients, proportions of individual nutrients in ileal chyme reflected those administered in the meal. Thus, it appears that malabsorption of lipids, proteins, and carbohydrates was roughly equal. Physiological malabsorption in healthy volunteers remained unaltered when enzymes (30 kU of lipase) were substituted together with the test meal. By contrast, in chronic pancreatitis patients, enzyme supplementation (pancreatin powder containing 30 kU of
lipase, 24 kU of amylase, and 2 kU of proteases) reduced malabsorption to 227 kJ—that is, by 50% (fig 9).104

In healthy volunteers, duodenal nutrients have a higher stimulatory potency compared with jejunal (see 2.2.9). In chronic pancreatitis, however, neither oral nor jejunal application of nutrients increased enzyme outputs,105,106 at least not in severe exocrine insufficiency.12 The effects of duodenal versus jejunal nutrient perfusion in chronic pancreatitis have not been compared, so far.

Ihse et al investigated pancreatic enzyme response to the Lundh test meal in 474 unselected patients including 42 patients with chronic pancreatitis.110 Depending on which enzyme the diagnosis was based, 80% to 90% of chronic pancreatitis patients showed varying degrees of pancreatic exocrine insufficiency (that is, lipase activity <185 U/ml, phospholipase activity <10 U/ml, trypsin activity <37 U/ml).

Addition of wheat bran or pectin to a Lundh meal further reduced intraluminal activities of endogenous as well as exogenously applied enzymes by 40% to 60%.116,117

Moreover, there is evidence that in chronic pancreatitis digestive enzyme output is not only reduced, but that the typical biphasic pattern of digestive enzyme release with an early postprandial peak followed by a decrease and a plateau phase (see fig 2) is almost lost. Instead, no or only a weak initial peak of intraduodenal enzyme activities was observed following the Lundh test meal in 47 patients with chronic pancreatitis.119

Overall, there are only a few studies investigating pancreatic exocrine response to mixed meals in chronic pancreatitis. Most of these have been performed as Lundh tests which include ingestion of a semiliquid, low caloric, easily digestible meal (15 g milk protein, 18 g corn oil, 40 g glucose, and 300 ml water; total 250.5 kcal, compare above) and it has to be kept in mind that this does not reflect normal Western diet. Compared with healthy subjects, pancreatic exocrine response to endogenous stimulation is decreased by 65% to more than 99% (table 4), probably depending on which patients are investigated.12 97 104 105 109 116 118 120

To prevent lipid malabsorption, lipase output has to exceed 5–10% of normal.116 Accordingly, in patients with virtually no enzyme secretion, it has been shown that administering sufficient enzymes into the duodenum and thus increasing lipase activities above 5% of normal is associated with abolition of steatorrhoea.121 The threshold activity that has to be exceeded throughout the digestive period is 40–60 U/ml of lipase.122 Taking normal ranges of lipase output and intraluminal lipase activity into account (see tables 1 and 2) and provided that postprandially nutrients will enter the duodenum for roughly four hours, a cumulative quantity of 25 000–50 000 U of exogenous lipase is required intraduodenally for digestion of a regular meal (5% of 2000–4000 U/min required for 240 minutes: 2000 U/min*0.05*240 minutes = 24 000 U, 4000 U/min*0.05*240 minutes = 48 000 U). Obviously, far higher doses of lipase supplements need to be administered orally, probably because of partial acidic destruction of enzymes particularly from non-enteric coated preparations and/or delayed, that is, partial jejunal release from modern, enteric coated preparations.122 As shown above, orally administered lipase at a dose of 28 000 IU only raised duodenal lipase to 1% of normal and did not normalise fat digestion.12 This suggests that with this specific enzyme preparation about 10 times more (that is, 280 000 IU) may still be required. However, it remains to be

Table 4 Pancreatic exocrine function in chronic pancreatitis

<table>
<thead>
<tr>
<th>Stimulus</th>
<th>Trypsin</th>
<th>Lipase</th>
<th>Amylase</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brugge et al, 1985109</td>
<td>CCK</td>
<td>10%</td>
<td>50%/23%/13%*</td>
<td>U, PL, phospholipase, El, elastase, CT, chymotrypsin</td>
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<td>Cornwell et al, 2002109</td>
<td>CCK</td>
<td>25%</td>
<td>65% [HCO3-]</td>
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</tr>
<tr>
<td>Cornwell et al, 2003114</td>
<td>CCK</td>
<td>20%</td>
<td>50% [HCO3-]</td>
<td></td>
</tr>
<tr>
<td>DiMango et al, 1973108</td>
<td>EAA</td>
<td>10%</td>
<td>10%</td>
<td></td>
</tr>
<tr>
<td>DiMango et al, 1973108</td>
<td>CCK</td>
<td>5%</td>
<td>15%</td>
<td></td>
</tr>
<tr>
<td>DiMango et al, 1977102</td>
<td>Mixed meal</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td></td>
</tr>
<tr>
<td>Funakoshi et al, 1990109</td>
<td>Mixed meal (intra-duodenally)</td>
<td>S+C</td>
<td>20%</td>
<td>30% [PL]</td>
</tr>
<tr>
<td>Hoeden et al, 1976110</td>
<td>S+C</td>
<td>10%</td>
<td>65% [HCO3-]</td>
<td></td>
</tr>
<tr>
<td>Ihse et al, 1977111</td>
<td>Lundh meal</td>
<td>25%†</td>
<td>30%†</td>
<td></td>
</tr>
<tr>
<td>Laver et al, 1997114</td>
<td>Lundh meal</td>
<td>30%†</td>
<td>20%</td>
<td></td>
</tr>
<tr>
<td>Makea et al, 1998111</td>
<td>S</td>
<td>30%</td>
<td>25% [PL]</td>
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<td>Mizuno et al, 1985117</td>
<td>S+P</td>
<td>60%/15%/35% [S]</td>
<td>60%/10%/45% [HCO3-]</td>
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<tr>
<td>Rogos et al, 1987112</td>
<td>EAA</td>
<td>50%</td>
<td>40%/50%/10% [El]</td>
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<tr>
<td>Rogos et al, 1988118</td>
<td>S+COX</td>
<td>50%</td>
<td>60%/10%/45% [CT]</td>
<td></td>
</tr>
</tbody>
</table>

Enzyme output in per cent of normal in response to various stimuli in patients with chronic pancreatitis. Data are partly derived from figures and therefore rounded.

CCK, cholecystokinin; EAA, essential amino acids; S, secretin; C, cerulean; P, pankreozymin; HCO3-, bicarbonate; PL, phospholipase; El, elastase; CT, chymotrypsin.

*Mild/moderate advanced chronic pancreatitis.
†Of lower limit of normal.
‡Mild advanced exocrine insufficiency.

Figure 9 Nutrient malabsorption with and without enzyme supplementation in healthy subjects (n = 14) and patients with chronic pancreatitis (n = 12).104
clarified whether this holds true for modern enzyme supplements, too.

3.2.3 Pancreatic response to protein, lipid, and carbohydrate diets

There are even fewer data on pancreatic exocrine response to individual food components in chronic pancreatitis. DiMagno et al compared pancreatic enzyme response to exogenous stimulation by CCK at a maximal stimulatory dose and to endogenous stimulation by essential amino acids (78 mM). In healthy volunteers, enzyme response to endogenous stimulation was weaker compared with exogenous stimulation by CCK. By contrast, in chronic pancreatitis, pancreatic exocrine response to both forms of stimulation was very low (about 10–20% of normal) but equal.105 Rogos et al also showed markedly reduced bicarbonate and enzyme secretion (about 50%) in response to duodenal essential amino acids compared with healthy volunteers.112

Literature research revealed only one study investigating the effect of duodenal fat perfusion on enzyme release in chronic pancreatitis: this study suggests that cumulative CCK release in response to duodenal free fatty acids is greater than to undigested triglycerides even in patients with severe pancreatic exocrine insufficiency according to the secretin-cerulein test. However, enzyme release was increased by duodenal nutrient exposure only in patients with moderate insufficiency. In contrast, the physiological enzyme response to duodenal free fatty acids was abolished in the patients with severe exocrine insufficiency and lowest residual secretory capacity.106

Similar to their effects on intraluminal enzyme activities in response to a mixed meal, pectin and wheat bran reduced cumulative 14C-exhalation following ingestion of a pure lipid meal (100 ml Intralipid) together with 1.5–2μCi 14C-triolein by about 30%.118 Moreover, dietary fibre inhibits pancreatic lipase activity by more than 50% in vitro.123 Thus, the decrease in digestive efficacy induced by intraluminal availability of pectin or wheat bran is probably induced by interactions between dietary fibres and activity of pancreatic enzymes rather than interactions between nutrients and fibres.

There appear to be no studies designed to investigate the effect of pure carbohydrate meals on pancreatic exocrine secretion in chronic pancreatitis, so far. Moreover, there are only indirect data on carbohydrate malabsorption following ingestion of a pure carbohydrate meal: using 14C breath tests and intestinal intubation studies, respectively, Ladas et al124 and Layer et al125 reported about 1% carbohydrate malabsorption in healthy volunteers following ingestion of 50–100 g rice starch. By comparison, about 10% malabsorption were observed in chronic pancreatitis patients.126 Conversely, Heile et al demonstrated that starch malabsorption occurred only when amylase secretion was 10% of normal or less.127 Data obtained by oro-ileal intubation and direct measurement of carbohydrate content in intestinal juice samples suggest that about 80% of carbohydrates are absorbed despite nearly complete experimental inhibition of amylase activity in healthy volunteers.128 Accordingly, even complete loss of amylase secretion in severe pancreatic exocrine insufficiency may reduce small intestinal carbohydrate digestion and absorption by only about 20%, although it remains unclear whether the degree of carbohydrate malabsorption is load dependent. Anyway, a considerable proportion of malabsorbed carbohydrates will be metabolised by the colonic flora and will not occur in stool.129 On the one hand, this represents a salvage mechanism by which considerable amounts of energy are gained. On the other hand, microbial metabolism of carbohydrates leading to production of gas and short chain fatty acids may contribute to symptoms such as diarrhoea, flatulence, and abdominal pain. The issue is further complicated by the fact that the rate of starch digestion by pancreatic amylase differs considerably, depending on starch species and/or its processing.76 130 Therefore, it remains open whether in chronic pancreatitis different nutrients have the same rank order of stimulatory potency as observed in healthy humans (that is, lipids > protein > carbohydrates; see 2.3–2.5). Moreover, the effects of different caloric content and of physical properties of a meal have not been investigated in chronic pancreatitis patients. Potential differences would probably be of minor clinical importance in patients with uncompensated or severe pancreatic exocrine insufficiency in whom enzyme substitution is needed under all circumstances to achieve sufficient nutrient digestion and absorption. By contrast, in patients with compensated pancreatic exocrine insufficiency such differences might influence integrated regulation of gastrointestinal secretory and motor functions and thereby determine whether patients develop gastrointestinal symptoms (fig 10).114 Although this hypothesis has not been tested in a specific experimental design, it is supported by several studies showing disturbed release of regulatory mediators and of upper gastrointestinal functions in response to experimental nutrient exposure of the distal small intestine110 111 126 and, most importantly, by studies showing correction or amelioration of gastrointestinal disturbances and/or symptoms by enzyme supplementation in chronic pancreatitis patients without overt steatorrhoea.106 132 133

3.2.4 Pancreatic response to exogenous stimulation

Most investigators performed various modifications of the secretin (S) or secretin cerulein (SC) test to examine pancreatic exocrine function in chronic pancreatitis. On the one hand, exogenous stimulation has the advantage of allowing estimation of the residual secretory capacity of the pancreas. On the other hand, alterations of gastrointestinal motor functions and of release of neurohormonal mediators in response to endogenous stimulation are neglected in these studies but are of importance for the pancreatic exocrine response to a regular meal as well as for development of symptoms.

As expected, chronic pancreatitis patients generally showed reduced bicarbonate and enzyme responses to exogenous stimulation (decreased by 40% to more than 98% compared with healthy controls; see table 4).106 107 108 110 111 114 Unlikely healthy controls, they demonstrated a progressive reduction in secretion during

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**Figure 10** Potential pathophysiological role of “compensated” pancreatic exocrine insufficiency for abdominal symptoms: in patients with mildly to moderately decreased exocrine function a distal shift of nutrient digestion and absorption may lead to impaired release of intestinal mediators. This, in turn may cause motility disturbances inducing abdominal symptoms and it may aggravate exocrine insufficiency. Accordingly, abdominal symptoms would not be a consequence of increased loss of nutrients but of a disturbance of the integrated regulation of gastrointestinal secretory and motor functions.
constant exogenous stimulation with secretin and cerulein for 90 minutes.120 Moreover, secretin infusion alone revealed pancreatic titis and showed that peak trypsin output during the SC test exogenous and endogenous stimulation in chronic pancreatitis. However, the comparability of the available data is hampered by inclusion of patients with varying aetiologies and degrees of pancreatic exocrine insufficiency, different modes of stimulation (secretin, CCK or its analogue cerulein, alone or in combination) for varying periods of time, as well as different doses of stimulatory agents.

DiMagno et al investigated pancreatic exocrine response to CCK in 16 healthy subjects and 16 patients with chronic pancreatitis. Infusion of CCK at a maximal stimulatory dose induced mean lipase and trypsin outputs of about 250 U/min and 60 U/min, respectively, in chronic pancreatitis patients, which was about 15–20% of normal. Nutrient malabsorption, that is, steatorrhoea and creatorrhoea, only occurred in patients in whom secretion of the respective digestive enzyme was below 10% of normal (that is, less than 167 U/min of lipase and 43 U/min of trypsin during stimulation with CCK).121 Kläss et al compared enzyme release in response to exogenous and endogenous stimulation in chronic pancreatitis and showed that peak trypsin output during the SC test correlated best with mean trypsin output during a Lundh test.122 Moreover, secretin infusion alone revealed pancreatic exocrine insufficiency in 85% of nearly 200 patients with definite or probable chronic pancreatitis.116 These data are in good agreement with the rate of exocrine insufficiency diagnosed in chronic pancreatitis by the Lundh test.97 In general, the degree of impairment of pancreatic exocrine function in chronic pancreatitis patients compared with healthy controls in response to exogenous stimulation was found to be similar to that observed in response to nutrients (table 4).105

3.2.4.1 Pancreatic exocrine function and morphological evidence of chronic pancreatitis

In patients with morphological evidence of chronic pancreatitis but with unknown pancreatic exocrine function, Brugge et al observed no increase in duodenal protein output in response to 40 ng/kg/h CCK octapeptide. By contrast, in healthy volunteers protein output was almost doubled.108 Rogos et al showed a 40–60% reduction of bicarbonate and enzyme output in response to a modified SC test compared with controls.122 Vice versa, Hardt et al observed that pathological faecal elastase-1 concentrations at a cutoff point of 200 μg/g had a positive predictive value of more than 95% for pancreatic duct abnormalities in more than 200 patients undergoing endoscopic retrograde cholangiopancreatography (ERCP), though sensitivity of elastase-1 measurements was low (45%).123 In addition, comparison of the results of the secretin test with ERP findings in 192 chronic pancreatitis patients revealed parallel results in about 75%, whereas impairment of exocrine function and morphologic alterations did not occur in parallel in about 25%, predominantly in patients with non-calculifying chronic pancreatitis.124 Similarly, Lankisch et al observed parallel SC test and ERP findings in 64% of 202 chronic pancreatitis patients, abnormal results in both tests but different degrees of severity in 21%, and totally non-parallel results in 15%.122 A normal ERP but abnormal SC test was observed in seven patients, that is, in about 3%. This means that pancreatic exocrine insufficiency without morphological alterations is rare, yet possible, as also shown by case reports.125

A recent study examined dilation of the main pancreatic duct in chronic pancreatitis patients and healthy volunteers in response to intravenous secretin by dynamic ultrasonography. Patients with definite or probable chronic pancreatitis had a lower maximal to basal duct diameter ratio than healthy subjects and this ratio correlated with bicarbonate output.126 Thus, the authors suggest that ultrasonographic findings might reflect pancreatic exocrine function and might be used for diagnosis.

3.2.4.2 Pancreatic enzyme pattern

Hoeden et al performed an SC test in 30 control subjects and 34 chronic pancreatitis patients. They observed that amylase output was decreased to 10% of normal whereas the trypsin output was less markedly reduced and was still about 40% of normal.119 Harada et al collected pure pancreatic juice in eight control subjects and 12 patients with chronic pancreatitis for 20 minutes after application of secretin and for a further 10 minutes following CCK. Maximal bicarbonate concentration and chymotrypsinogen output were decreased in all chronic pancreatitis patients and appeared to be most susceptible followed by maximal lipase output and peak chymotrypsinogen concentration. Amylase was slightly less affected.127 In contrast, Mizuno et al observed that exogenously stimulated chymotrypsin and lipase release were reduced to a similar extent in mild and severe disease, and that both were reduced slightly more than trypsin and amylase in severe disease but that elastase output was the most affected by pancreatic disease including chronic pancreatitis.128 Yet, there are further studies suggesting that lipase secretion is most susceptible to chronic pancreatitis and is impaired earlier and more severely compared with secretion of other enzymes.97 142 In particular, DiMagno et al showed that in most of 17 patients with chronic alcoholic pancreatitis, lipase output was reduced to a slightly greater extent compared with trypsin output. On the other hand, there were only two patients with lipase output below and trypsin output above 10% of normal associated with steatorrhoea but not creatorrhoea.144 However, regression curves drawn from these data suggest that in chronic alcoholic pancreatitis lipase secretion may reach the critical threshold of 10% of normal 5–10 years before trypsin output.2 Similarly, Ilse et al showed a significantly reduced lipase: trypsin ratio in 42 patients with chronic pancreatitis compared with 133 healthy controls.97

Taken together, there are single studies suggesting that amylase,109 chymotrypsin,146 or elastase107 secretion may be impaired earlier and/or more severely in chronic pancreatitis compared with secretion of other components of pancreatic juice whereas two studies show that lipase secretion is particularly susceptible.117 142 Still, there is only one study comparing release of all major pancreatic hydrolyses—that is, lipase, amylase, trypsin, and chymotrypsin—in chronic pancreatitis.122 Furthermore, varying sensitivity and accuracy of enzyme assays hamper comparability. Thus, it has not been fully clarified whether secretion of all pancreatic enzymes is reduced more or less in parallel in chronic pancreatitis or whether secretion of an individual enzyme, especially lipase, is particularly susceptible.

3.2.5 Pathophysiological mechanisms contributing to steatorrhoea

From a clinical point of view, steatorrhoea remains the most prominent digestive malfunction in pancreatic exocrine insufficiency: it may be associated with malabsorption of the lipid soluble vitamins A, D, E, and K, it is usually more severe, and develops several years before overt malabsorption of protein or starch.2 95 143 The earlier disturbance of fat absorption is caused by several interacting mechanisms:
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Firstly, the question of whether the capacity of the pancreas to synthesise and secrete lipase is impaired earlier and more severely in the course of chronic pancreatitis compared with other enzymes has been extensively discussed above. Theoretically, in the same patient, a decrease in lipase secretion to less than (5% to 10)% of normal may cause steatorrhoea for several years earlier, while protease output may be maintained in a range between 10–20% of normal which is supposed to be sufficient to prevent protein malabsorption.12,121

Secondly, pancreatic bicarbonate secretion, which serves to protect pancreatic enzymes from denaturation by gastric acid, is also diminished in exocrine pancreatic insufficiency (see 3.2.6). Low intraduodenal pH dramatically reduces lipase activity (only 50% activity at pH 7 compared with pH 9). In severe exocrine pancreatic insufficiency intraduodenal pH falls to around 4, particularly late postprandially.12 Lipase is very susceptible to acidic destruction12 and, therefore, the small residual quantities of lipase secreted into the duodenum may be inactivated.1 In addition, bile acids are precipitated by low intraduodenal pH levels and lipid absorption is compromised further.146

Thirdly, lipase degradation within the small intestinal lumen occurs more rapidly than destruction of other enzymes due to its greater instability against proteolysis.147,148 This means that, compared with other enzymes, lipase activity is available for a shorter period of time during small intestinal transit in healthy individuals149 as well as in patients with exocrine pancreatic insufficiency.147

Fourthly, extrapancreatic lipolytic enzymes, which have been shown to be entirely of gastric origin,150 contribute only little to overall lipid digestion in humans.40,55,145–148 There is evidence that in pancreatic exocrine insufficiency the relative importance of gastric lipase for lipid digestion is increased—that is, gastric lipase may digest more than 50% instead of roughly 20% of dietary fat.15 However, most studies available suggest that secretion of gastric lipase cannot be upregulated to compensate for the loss of pancreatic lipase.145,149 By contrast, a recent study by Carriere et al showed a three to fourfold increase in gastric lipase output.149 Astonishingly, intragastric lipolysis levels did not increase accordingly, but even tended to be lower than in healthy volunteers (4.8% (SD 1.2%) v 7.3% (5.9%) of meal triglycerides converted into free fatty acids and monoglycerols). This seemingly paradoxical effect was potentially due to lower intragastric pH or accelerated gastric emptying and reduced time for digestion.104,120,150 Furthermore, there are contradictory data whether in chronic pancreatitis gastric lipase secretion is increased adequately in response to physiological stimuli (that is, gastrin or cephalic stimulation).151–153 Within the intestinal brush border, there are no triglyceride digesting enzyme systems. Consequently, adequate lipid digestion within the small intestinal lumen depends on the interaction of pancreatic lipase and its cofactors—that is, colipase and bile acids. A decrease in pancreatic lipolytic activity cannot be compensated sufficiently by other mechanisms. By contrast, protein digestion is maintained even if virtually all luminal pancreatic proteolytic activity is blocked under experimental conditions because protein digestion is initiated by intragastic proteolytic activity and continued by the intestinal brush border peptidases. It has to be remembered, however, that small intestinal protein malabsorption in chronic pancreatitis may be considerably underestimated because malabsorption and malabsorption are measured in the faeces and there is rapid hindgut fermentation of any unabsorbed protein. Similarly, in the absence of pancreatic amylase activity, starch digestion is delayed, but can be achieved to about 80% by salivary amylase and by brush border oligosaccharidases.145 Furthermore, a considerable proportion of malabsorbed carbohydrates is metabolised by the colonic flora and does not occur in stool.127–129

Lastly, there is evidence that biliary secretion may be particularly susceptible to and impaired by inhibitory influences of ileal nutrient exposure as expected in pancreatic exocrine insufficiency.131 Decreased release of bile acids may further compromise lipid digestion and absorption.

3.2.6 Bicarbonate output and duodenal pH

In chronic pancreatitis, the chronic inflammatory process does not only destroy pancreatic acini but also the ductal tissue and thereby impairs bicarbonate secretion. Decreased bicarbonate secretion eventually results in decreased duodenal pH. This is of importance not only because neutral to basic intraluminal pH is a prerequisite for optimal activity of digestive enzymes,134 but also because pancreatic enzymes, in particular lipase, can be inactivated irreversibly by acidic pH (that is, pH <4).12 This further compromises lipid digestion and is true for both residual endogenous enzyme secretion and therapeutic enzyme supplementation. Most investigators concentrated on measuring outputs of digestive enzymes in chronic pancreatitis but bicarbonate output may also be used as a marker of pancreatic exocrine dysfunction.145 However, those studies which compared enzyme and bicarbonate output in chronic pancreatitis suggest that bicarbonate secretion may be preserved longer than enzyme secretion and, thus, may be less sensitive.145

DiMagno et al showed that in chronic pancreatitis postprandial duodenal pH was lower than in healthy subjects and reached the threshold for lipase inactivation (that is, pH 4) late postprandially. By contrast, interdigestive and early postprandial duodenal pH were within the physiological range.104 Accelerated gastric emptying may contribute to low intraduodenal pH in chronic pancreatitis.104,120 Its relative contribution has not been estimated, so far, but the observations that late gastric emptying was accelerated in particular104 and that duodenal pH was particularly low in chronic pancreatitis patients late postprandially120 underline the potential importance of disturbed gastric emptying in chronic pancreatitis. On the other hand, direct measurements showed no statistically significant difference between duodenal acid delivery in chronic pancreatitis patients with varying degrees of pancreatic exocrine insufficiency compared with five healthy controls despite accelerated gastric emptying in patients.120

Gastric acidity also appears to be associated with pancreatic exocrine function: Bovo et al observed an earlier drop in intragastric pH postprandially in patients with uncompensated compared with compensated pancreatic exocrine insufficiency.155 Moreover, there was a positive correlation between median postprandial pH and lipase output. If gastric contents were not aspirated completely, this may not only be explained by the association between the degree of pancreatic exocrine insufficiency and the drop of intragastric pH but also by acidic destruction of lipase intraduodenally. Following a low caloric, low fat meal (300 ml chocolate milk, 5% protein, 5% carbohydrates, 1.5% fat, 660 kJ), a poor correlation between continuously measured (in vivo) jejunal pH values and pH in jejunal aspirates (in vitro) was observed in chronic pancreatitis patients and healthy controls.144 However, from the experimental protocol it does not become clear whether pH of aspirates was measured adequately. Only for in vivo measurements, a longer period with pH below 4 was demonstrated in uncompensated pancreatic exocrine insufficiency. Moreover, it was shown in this study that the fraction of bile acids in the micellar phase of duodenal contents correlated with duodenal pH and the fraction of fat solubilised. Accordingly, acidic bile acid precipitation
probably plays a major role for steatorrhoea in chronic pancreatitis.\textsuperscript{144} 156

3.2.7 Summary
Takken together, in an unselected group of patients with chronic pancreatitis 80% to 90% show some degree of pancreatic exocrine insufficiency and mean pancreatic exocrine function is reduced by about 50% to 80% compared with healthy volunteers. In about 65% to 75% of patients, morphological alterations and functional impairment occur in parallel. Pancreatic exocrine insufficiency without morphological alterations is rare (less than 5%), yet possible.

There is evidence that the pancreatic enzyme pattern is altered in chronic pancreatitis, but it is controversial which component of pancreatic juice is most susceptible. Two studies suggest an earlier and stronger impairment of lipase secretion compared with secretion of other enzymes. The observation that lipid malabsorption is the most important digestive dysfunction in chronic pancreatitis is further explained by impaired bicarbonate output, which causes more rapid and complete inactivation of lipase and bile acid precipitation within the acidic duodenum, by greater susceptibility of lipase against proteolytic destruction, by low effectiveness of compensating enzyme systems, and by potent inhibition of biliary output in response to malabsorbed nutrients. Moreover, faecal nutrient excretion is considerably influenced by fermentation of carbohydrates and protein by colonic bacteria.

Apart from an overall reduction in enzyme release, the physiological biphasic postprandial pattern and differential responsiveness to varying degrees of endogenous and exogenous stimulation appear to be lost in chronic pancreatitis. In decompensated chronic pancreatitis with less than 5% of normal enzyme output, about 40% of nutrients of an easily digestible low caloric meal are malabsorbed and enter the colon. Proximal small intestinal enzyme activities can be increased and malabsorption can be decreased by enzyme supplementation. However, even with clinically established doses of pancreatin (28 kU of lipase) duodenal lipase delivery remains far below the physiological range and lipid malabsorption cannot be normalised.

3.3 Acute pancreatitis
Data from animal studies have shown that the exocrine function of the pancreas during acute pancreatitis is decreased.\textsuperscript{153–156} For methodological and ethical reasons, only the interdigestive, non-stimulated exocrine function could be determined in humans during the acute phase of the disease. Interdigestive pancreatic exocrine secretion was shown to be variable (normal in most cases, decreased or increased in individuals) in the early phase of mild to moderate acute pancreatitis.\textsuperscript{163} 164 and was adequately reduced by glucagon and cimetidine.\textsuperscript{164}

It is controversial whether (recurrent) acute pancreatitis has long term effects on pancreatic exocrine function. During the subacute phase and during convalescence, reduced pancreatic exocrine function was shown in all patients investigated even by less sensitive indirect pancreatic function tests (PABA test).\textsuperscript{153} 156 By contrast, patients who had recovered from an attack of acute pancreatitis two to six years before showed normal results in this test.\textsuperscript{155} More sensitive measurements of stimulated enzyme synthesis and turnover in 10 patients with acute pancreatitis two to 29 months after the most recent attack showed non-parallel changes with decreased total protein and amylase but preserved trypsin synthesis and turnover. The authors suggest that there may be continuing acinar cell malfunction and specifically impaired amylase synthesis following acute pancreatitis.\textsuperscript{167}

Similarly, Bozkurt et al observed mostly mild to moderate pancreatic exocrine insufficiency in 80–85% of 53 patients who had recovered from their first attack of necrotising acute pancreatitis. Functional impairment persisted for at least 18 months, though severe forms appeared to be less frequent in the long term group (6%) compared with a group of patients investigated after four weeks (26%).\textsuperscript{168} Boreham and Ammori found a similar rate of pancreatic exocrine insufficiency—that is, 86% in patients recovering from necrotising acute pancreatitis. In general, development of exocrine insufficiency correlated strongly with the extent of pancreatic necrosis and the severity of pancreatic endocrine insufficiency (fig 11). During the four week observation period, there was no recovery of exocrine function in patients with necrotising disease.\textsuperscript{169} Further investigations by Seidensticker et al, including patients with less severe forms of acute pancreatitis up to 156 months after the acute attack, showed normal pancreatic exocrine function and a normal ERCP in 50% of patients. Functional impairment with \((n = 4)\) or without \((n = 1)\) morphological alterations was observed in 13% of patients. Interestingly, all of these patients later developed chronic pancreatitis.\textsuperscript{170}

3.3.1 Summary
In summary, little is known about the secretory capacity of the pancreas during the acute phase of acute pancreatitis and ethical reasons will probably prevent such investigations. During the subacute phase (the first few weeks following an acute attack), pancreatic exocrine function appears to be regularly impaired and a considerable percentage of patients with necrotising disease may show severe exocrine insufficiency. Depending on the severity of acute pancreatitis and the degree of pancreatic necrosis, pancreatic exocrine function recovers step by step, but in a subset of patients exocrine insufficiency may last for several months or may even persist permanently.

3.4 Pancreatic cancer
Obstruction of the pancreatic duct by tumours of the head of the pancreas, ongoing destruction of the normal pancreas by tumour growth, and loss of pancreatic tissue following surgical procedures frequently cause pancreatic exocrine insufficiency in pancreatic carcinoma. Studies with pancreatic carcinoma describing the quantitative relations between the length of opacified main pancreatic duct obtained at ERCP and the secretory capacity of the exocrine pancreas revealed that secretion did not decrease until more than 60% of the total length was obstructed. As the site of pancreatic cancer further approached the duodenum, enzyme secretion decreased in an exponential fashion (fig 12).\textsuperscript{171} Ihs
et al performed a Lundh test in 474 unselected patients including 25 with pancreatic carcinoma. Of these, depending on the enzyme analysed, 80–90% showed exocrine insufficiency. Furthermore, a significant decrease in lipase:trypsin and lipase:phospholipase ratios and loss of the typical biphasic secretory pattern were observed. These findings suggest that similar to chronic pancreatitis, pancreatic cancer not only decreases pancreatic exocrine secretion but may also alter enzyme pattern. The rate of exocrine insufficiency observed in this study matches well with data obtained by Perez et al showing malabsorption in 85% of patients with pancreatic cancer.175 In 14 preoperative patients with pancreatic tumours, and 13 patients who had undergone pancreatoduodenectomy more than five years ago, an indirect pancreatic function test—the $^{13}$C-trioctanoin breath test—revealed impaired lipid digestion and absorption in all cases. Not surprisingly, direct measurement of pancreatic exocrine secretion by the secretin test showed pathological results in 13 out of 14 patients preoperatively and in four out of five postoperatively.175

3.4.1 Summary
Overall, there is a limited number of studies revealing exact information about pancreatic exocrine function in patients with pancreatic cancer. This is probably due to the poor prognosis of these patients which limits reasonable investigations. Available evidence suggests exocrine dysfunction and malabsorption in 80–90% of patients potentially associated with loss of the normal secretory pattern. The site and degree of ductal obstruction appear to be major determinants of residual pancreatic exocrine secretion.

3.5 Cystic fibrosis
In cystic fibrosis, an autosomal recessive defect of the gene that encodes for the cystic fibrosis transmembrane regulator (CFTR), a cyclic AMP regulated chloride channel impairs water secretion of exocrine glands including the pancreas.174 Highly concentrated and viscous pancreatic juice blocks the pancreatic ducts leading to acinar atrophy, fibrosis, fatty replacement, and inspissation of secretions in ducts and acini.175 More recent data suggest that acidification of luminal contents of pancreatic tissue, due to disturbed bicarbonate release, may be an important mechanism leading to defects in apical trafficking of zymogen granules and of solubilisation of enzymes with subsequent cytological alterations.176 Even if compared with controls matched for pancreatic exocrine function as defined by trypsin secretion, cystic fibrosis patients secrete significantly less fluid (mean water secretion 3.35 ml/kg/h v 9.74 ml/kg/h in controls) and their pancreatic secretions are hyperconcentrated.177 Moreover, a significant linear correlation was observed between protein output and volume secretion in cystic fibrosis patients only, suggesting that fluid secretion may be a rate limiting factor in protein output.177 Pancreatic exocrine insufficiency of varying degrees was observed in 55–100% of patients. Weizman et al demonstrated reduced enzyme output in all of 18 cystic fibrosis patients compared with mean output of healthy subjects. However, only in seven out of 18—that is, 39%—was it severe enough to cause steatorrhoea. Similarly, Walkowiak et al reported some degree of pancreatic exocrine insufficiency in all of 28 cystic fibrosis patients investigated by the secretin cholecystokinin test; in 20 of these (about 70%) it was severe and, thus, presumably associated with malabsorption.180 Most recent studies agree that (severe) pancreatic exocrine insufficiency occurs in more than 80% of cystic fibrosis patients.176 182 183 Differing results might be explained by the varying age of the subjects investigated because some studies report increase in frequency and degree of pancreatic involvement over time, particularly during the first months and years of life.184 Others, however, already found pancreatic involvement in 85–95% of one year old children in various populations.185 Moreover, the probability of pancreatic insufficiency depends on the underlying gene defect (particularly high in patients with ∆F508 mutation).186 187 In general, patients who carry two “severe” gene mutations develop pancreatic insufficiency, whereas those who carry at least one “mild” mutation usually remain pancreatic sufficient (fig 13). These represent about 10% of patients. However, the latter does not exclude pancreatic insufficiency.187

Pancreatic enzymes involved in lipid digestion such as lipase, colipase, and phospholipase were decreased in parallel in children with cystic fibrosis.188 Impaired pancreatic lipase secretion might in part be compensated by a moderate increase in gastric lipase activity and intragastric lipolysis.189 Duodenal pancreatic enzyme output in response to a meal or meal components has rarely been studied in cystic fibrosis, probably because of the invasive character of these investigations and the young age of most patients. Augarten et al examined serum lipase levels before and after pancreatic stimulation by a Lundh meal in 36 cystic fibrosis patients with severe pancreatic exocrine insufficiency, eight patients with mild disease and normal exocrine function, and 17 healthy individuals. The authors claim that consistently low lipase levels suggested a severely affected insufficient pancreas; normal basal levels followed by a linear rise peaking 30 minutes after the meal reflected normal exocrine function. Increased lipase levels not influenced by the meal were found in five out of eight patients with mild disease and were interpreted as an ongoing destructive process in the pancreas which will eventually result in conversion from pancreatic sufficiency to pancreatic insufficiency.189 However, these conclusions appear premature and findings have so far not been confirmed.
Similarly, the number of studies on nutrient digestion and absorption is limited. In an early study, average fat absorption was found to be 46% of the amount ingested in 12 children without pancreatic enzyme supplementation, 67% in response to 5 g pancreatin four times daily and 71% in response to 15 g pancreatin.140 With modern therapeutic strategies using more recently developed pancreatic preparations nutrient absorption can be increased,140 141 although seldom normalised.141

One reason for this presumably is that even modern pancreatic enzyme supplements do not fully imitate physiological intraluminal enzyme activities.142 On the other hand, further disturbances of gastrointestinal secretory and motor functions apart from pancreatic insufficiency—that is, alterations of gastrointestinal pH, motility, and transit—are observed in cystic fibrosis and may additionally compromise assimilation of nutrients.140

Basal and stimulated gastric acid secretion were reported to be greater in cystic fibrosis than in healthy controls, but this was contradicted by others and did not affect interdigestive or postprandial gastric pH.143 Fasting and postprandial duodenal pH were 1–2 pH units lower in cystic fibrosis patients (range 3–6 postprandially) than in control subjects (range 5–7 postprandially), probably mainly due to reduced pancreatic bicarbonate secretion.144 Whether impaired duodenal bicarbonate release contributes to low intraluminal pH is not clarified, yet. PH of luminal contents in the more distal small intestine of cystic fibrosis patients—that is, in the jejunum and ileum—was seldomly measured and was reported to be slightly lower or similar to that in healthy subjects.145 Increasing intraluminal pH by treatment with omeprazole improves fat absorption in enzyme treated patients.146 147 148 This may not only be due to better survival of exogenous enzyme preparations but also to improved conditions for lipolysis by endogenous gastric lipase.149 150 In cystic fibrosis patients with severe pancreatic exocrine insufficiency gastric lipase accounted for about 90% of total lipolytic activity at the ligament of Treitz151 as opposed to 7% in healthy volunteers.152

Available data suggest that gastric emptying of liquid meals is normal or accelerated in cystic fibrosis.153 Gastric emptying of solids, which is more susceptible to impairment, was not adequately investigated in these patients, so far. Taylor et al report a discrepancy between the gastric emptying of microspheres (supposed to simulate modern enzyme preparation) and a standard pancake and baked beans test meal. The half time of gastric emptying of 103 minutes appears to be within the normal range; unfortunately, however, no normal values were given by these investigators.154 Symonds et al found similar gastric emptying of solids in children with cystic fibrosis and healthy controls using the 13C-octanoic acid breath test. Remarkably, those patients with slow gastric emptying had less improvement of fat digestion and absorption than patients with a high gastric emptying velocity.155

Small intestinal motility has never been measured directly in a group of cystic fibrosis patients; instead, several investigators studied orocecal transit using the lactulose H2 breath test and observed prolonged orocecal transit times compared with healthy controls.156 157 158 This is at variance with what we observed in chronic pancreatitis patients159 and may be due to cystic fibrosis specific small intestinal motility disturbances. However, altered colonic flora caused by chronic use of antibiotics to combat respiratory infections likely decreases reliability of the lactulose H2 breath test and questions these findings. Increased plasma levels of motilin, enteroglucagon, neurotensin, and PYY in cystic fibrosis160 161 may at least in part account for gastrointestinal motor dysfunction and may also impair gastrointestinal secretory functions. Overall, disturbances of gastrointestinal motility and of release of regulatory mediators may aggravate maldigestion and malabsorption in cystic fibrosis.

3.5.1 Summary
In conclusion, a well characterised hereditary defect of electrolyte and water secretion induces major morphological alterations of the pancreas in the majority of patients with cystic fibrosis leading to functional impairment. According to recent studies severe pancreatic exocrine insufficiency is observed in more than 80% of patients. Nutrient digestion and absorption is markedly increased by enzyme supplementation with or without suppression of gastric acid secretion; however, it is rarely normalised. This may in part be due to the fact that in cystic fibrosis further disturbances of gastrointestinal secretory and motor functions—that is, alterations of gastrointestinal pH, motility, and transit—additionally compromise assimilation of nutrients.

3.6 Gastrointestinal surgery
3.6.1 Pancreatic resections
Major pancreatic resection naturally decreases pancreatic secretory capacity and it depends on the original disease process and on the type and extent of resection whether patients develop maldigestion and malabsorption. Following middle segment pancreatectomy, a novel technique reported recently for conserving pancreatic tissue, none of 10 patients operated on because of benign pancreatic tumours of the neck or body of the pancreas required pancreatic enzyme supplements postoperatively.162 Drainage procedures,163 164 165 166 segmental resection,167 and duodenal preserving pancreatic head resection (DPPHR),168 169 170 did not decrease pancreatic exocrine function compared with preoperative values. Even in patients followed up for up to 26 years after DPPHR, the rate of patients requiring enzyme supplementation postoperatively remained more or less stable.171 Drainage procedures with or without (minor) resections were even found to
be associated with improvement of exocrine function in a subset of patients. By contrast, following conventional pancreaticoduodenectomy or pylorus preserving pancreaticoduodenectomy (PPPD) patients showed about a 20% decrease in the PABA test or decreased faecal chymotrypsin. In the latter patient group, insufficient weight gain despite intake of regular amounts of pancreatin was shown to be associated with decreased pancreatic exocrine function postoperatively.

Children with previously normal exocrine function operated on because of necrobiotic pancreatitis generally showed normal pancreatic enzyme activity and bicarbonate concentrations following a 75% pancreatic resection. Even a 95% pancreatic resection was tolerated without clinically significant exocrine failure in six out of seven patients. These findings underline the enormous functional reserve capacity of the healthy exocrine pancreas.

On the other hand, short term effects of pancreatic head resection appear to depend on the preoperative findings: residual pancreatic exocrine function after operation was associated with the preoperative degree of pancreatic fibrosis and pancreatic exocrine function deteriorated early postoperatively only in a group of patients with markedly dilated pancreatic duct but not in those with normal duct diameter. Within 12–31 months, pancreatic exocrine function recovered to preoperative levels in both groups. Progression of the underlying disease accounted for failure of both exocrine and endocrine functions on long term follow up following partial pancreatic resections.

Moreover, in patients with preexisting chronic pancreatitis, the percentage of patients with steatorrhoea was increased from 3.7% to 19% by 40–80% distal resection, from 9.0% to 37.6% by 80–95% distal resection and from 5.2 to 55% by Whipple’s operation. The average faecal loss of fat following a 80–95% distal resection in patients ingesting 100 g fat per day was 26.4 g/d (normal: less than 5–7 g/d), that is, the coefficient of fat absorption in these patients was reduced to 73.6% compared with greater than 93–95% in healthy humans.

Residual lipid digestion in spite of almost complete loss of pancreatic exocrine tissue is probably due to gastric lipase (see 2.6.2).

It has to be kept in mind, however, that most of the favourable data on the effects of partial pancreatic resection on pancreatic exocrine function cited above have been obtained by rather crude methods which only allow reliable diagnosis of severe pancreatic exocrine insufficiency. Data from animal experiments using direct measurements of pancreatic protein, enzyme, and bicarbonate output in pancreatic juice showed decreased secretion in response to endogenous and exogenous stimulation in partially pancreaticomised dogs and in rats following extensive resections.

Human studies describing the quantitative relations between the length of opacified pancreatic duct obtained at ERCP and the secretory capacity of the exocrine pancreas revealed that 40% of the gland (pancreatic head) can secrete enzymes and bicarbonate at normal rates.

3.6.2 Gastric resections

Not only surgical procedures of the pancreas but also partial or total gastrectomy may be associated with intraluminal lack of pancreatic enzymes postprandially, mainly because of asynchrony between gastric emptying of the meal and discharge of bile and pancreatic enzymes into the small intestine (postcibal asynchrony). As digestive products are stronger endogenous stimulators of CCK release and of pancreatic secretion than macronutrients, postcibal asynchrony is also associated with decreased endogenous stimulation (fig 8).

There is evidence however, that further mechanisms may contribute to pancreatic insufficiency following gastric surgery. Friess et al investigated 15 patients undergoing total gastrectomy due to gastric cancer. A secretin cerulein test was performed preoperatively and endocrine responses to a test meal were measured. In nine patients, both tests were repeated postoperatively. All patients had normal pancreatic function preoperatively. Postoperatively, all patients were assessed as having severe pancreatic exocrine insufficiency and secretion of pancreatic juice, trypsin, chymotrypsin, and amylase was reduced by 70–90% (fig 14). These findings cannot be explained by postcibal asynchrony but suggest “direct” pancreatic influences. Furthermore, pancreatic insufficiency was more severe than described in previous studies. The authors attribute severe impairment of pancreatic exocrine function to the extensive denervation of the pancreas because of lymph node dissection and truncal vagotomy. The latter has been shown to cause mild to moderate pancreatic exocrine insufficiency (reduction of secretin stimulated trypsin and lipase outputs by 50–60%) by itself.

Heptner et al observed primary pancreatic exocrine insufficiency following gastric resection for various reasons in only 30% of patients. By contrast, the Pankreolauryl test (Tremmler Pharma GmbH & CO KG, Marburg, Germany), an indirect pancreatic function test which allows estimation of intraluminal digestion of a test meal, was abnormal in 90% of these patients postoperatively, probably as a result of interacting pathomechanisms (“primary” insufficiency, postcibal asynchrony, decreased endogenous stimulation, fig 8).

3.6.3 Short bowel syndrome

Following extensive small bowel resections, reduced endogenous stimulation and postcibal asynchrony may lead to intraluminal pancreatic enzyme deficiency and may thereby reduce nutrient absorption. Therefore, administration of pancreatin preparations is encouraged by several authors although there are no controlled studies demonstrating a positive effect of enzyme supplementation therapy. Theoretically, application of unprotected pancreatic enzymes together with gastric acid suppression therapy should enable gastric digestion of nutrients with increased delivery of digestive products to the small bowel. Because of the superior stimulatory capacity of peptides, amino acids, and free fatty acids compared with macronutrients, conditions for nutrient absorption should be improved by increased endogenous pancreatic enzyme secretion, delayed gastric emptying, and small intestinal transit as well as mucosal hypertrophy (fig 15).
Pancreatic exocrine dysfunction is observed in a subset of patients with coeliac sprue although it is generally assumed that the pancreas is not involved. In coeliac disease patients, decreased release of stimulatory mediators, in particular CCK\(^{231, 232}\) from the atrophic proximal small intestinal mucosa explains diminished endogenous stimulation\(^{231}\) and asynchrony between transit of the meal and discharge of bile and pancreatic enzymes into the small intestine (fig 8). It is assumed that these pathomechanisms interact and lead to intraluminal lack of digestive enzymes and malabsorption despite normal secretory capacity of the pancreas.\(^{233, 234}\) Accordingly, DiMagno et al observed equal enzyme output during exogenous stimulation with CCK in healthy volunteers and coeliac patients, whereas in the latter, enzyme output was decreased by more than 50% during endogenous stimulation with essential amino acids.\(^{235}\)

In untreated coeliac patients, pancreatic exocrine insufficiency was observed in 15–40%,\(^{237, 238}\) In most cases, insufficiency was mild to moderate. In less than 10% of patients pancreatic secretion was below 10% of normal—that is, severely impaired.\(^{233, 235}\) Generally, pancreatic exocrine insufficiency is limited to patients with mucosal damage and reversed by restitution of the intestinal mucosa after initiation of gluten free diet.\(^ {235, 238}\) There is even evidence that pancreatic function is indirectly related to the degree of damage of the duodenal and jejunal mucosa in coeliac disease.\(^ {237, 238}\) Moreover, recent findings suggest that exocrine pancreatic secretion is decreased in villous atrophy regardless of the underlying disease.\(^{241}\) Accordingly, abnormal pancreatic function was found in about 65% of patients with untreated tropical sprue using an indirect test and probably was also due to low pancreatic neurohormonal stimulation because of intestinal damage.\(^{242}\)

However, in contrast to what has been discussed above, several more recent studies report decreased pancreatic exocrine response to exogenous stimulation in coeliac disease.\(^ {232, 235–237, 240, 241}\) Severe exocrine insufficiency with residual enzyme secretion rates below 10% of normal was rare (about 8% of patients), but subnormal values for one or more pancreatic enzymes were observed in nearly one third of patients.\(^ {237}\) These findings question the concept that lack of endogenous stimulation and postprandial asynchrony due to mucosal damage are the only causes of pancreatic dysfunction in coeliac disease. Instead, they might point to coexisting pancreatic disease and may explain failure of dietary treatment (gluten free diet) in a subset of patients.\(^ {232, 233, 235–238, 240, 243–246}\)

Caroccio et al divided 52 coeliac disease patients into three groups according to their weight/height ratio (<3rd percentile, 4–10th percentile, >10th percentile). They observed no differences in enzyme outputs between these groups and concluded that mild to moderate pancreatic exocrine insufficiency is rather frequent in coeliac disease patients, but possibly completely independent of the nutritional status and probably of little clinical importance.\(^ {237}\) By contrast, the same group observed a faster weight gain in coeliac patients receiving enzyme substitution together with a gluten free diet compared with patients receiving the diet only during the first 30 days of therapy.\(^ {236}\) In addition, they reported a positive correlation between faecal chymotrypsin at diagnosis of coeliac disease and weight gain within the first 60 days of therapy.\(^ {237}\) Consequently, faecal chymotrypsin could predict weight recovery within the first two months after diagnosis of coeliac disease and low faecal chymotrypsin could be used to select patients who probably benefit from enzyme treatment.\(^ {237}\) It remains unclear why low chymotrypsin was not correlated with low body weight at diagnosis but with slow weight gain during gluten free diet.\(^ {238}\)

Another interesting and so far unexplained finding is that the pattern of pancreatic exocrine secretion (for example, ratios among pancreatic enzymes) appears to be altered in coeliac patients.\(^ {232, 234, 240}\) Lipase secretion was found to be decreased whereas trypsin secretion remained more or less stable leading to a decrease in the lipase:trypsin ratio.
diseased upper intestinal mucosa leading to reduced enzyme and bicarbonate secretion and postcibal asynchrony of secretory and motor functions. Still, it remains unclear whether these are the only pathomechanisms or whether there may be direct pancreatic insufficiency in a subset of patients. At least in children with coeliac disease, low faecal chymotrypsin might be used to select patients who would probably benefit from enzyme treatment during the first few weeks of therapy.

3.8 Diabetes mellitus

In diabetic patients, marked morphological alterations of the exocrine pancreas are observed. Compared with healthy controls, the pancreas of patients with diabetes was smaller, mainly caused by involution of the exocrine tissue. Atrophy particularly affected the pancreatic body and was more pronounced in insulin dependent diabetes mellitus patients (IDDM) compared with non-insulin dependent diabetics (NIDDM). Diabetes treated with, but not fully dependent on, insulin showed intermediate reductions in pancreatic size. It is controversial as to whether morphological alterations correlate with the duration or the age at onset of the disease. Histopathological alterations were more pronounced in IDDM and included pancreatic fibrosis, fatty infiltration, and intra- and perirectal inflammatory infiltrates in IDDM. Lymphocytic insulitis, a predominant characteristic of IDDM, disappeared after the beta cells had been totally destroyed.

In addition to morphological alterations, a considerable proportion of patients with diabetes mellitus show mild to moderate impairment of bicarbonate and enzyme secretion. In IDDM, a strong correlation was observed between pancreatic volume measured by computed tomography and exocrine function—that is, patients with small pancreata had low exocrine function. This correlation was only weak in NIDDM. Moreover, prevalence of pancreatic exocrine insufficiency is particularly high in IDDM and ranges between about 40 to 80% in these patients. For these investigations various modifications of the secretin pankreozymin test or faecal elastase-1 measurements were applied. Our own study in 12 IDDM patients confirmed that overall pancreatic enzyme secretion was decreased, however, the degree of impairment varied among different enzymes (fig 16): amylase output was normal in the interdigestive state during moderate endogenous and maximal exogenous stimulation. Diminished fasting lipase output increased regularly in response to endogenous but not to exogenous stimulation. Apparently, chymotrypsin output was most susceptible and was decreased under all experimental conditions. Consequently, pancreatic enzyme pattern appears to be altered in response to different stimuli in IDDM. Chymotrypsin secretion may be most susceptible to IDDM associated disturbances. In contrast, we observed markedly decreased amylase output in response to maximal exogenous stimulation in a mixed group of IDDM and NIDDM patients without clinical evidence of pancreatic exocrine insufficiency.

In NIDDM patients, the prevalence of pancreatic exocrine insufficiency estimated by various modifications of the secretin pankreozymin test or faecal elastase-1 measurements is somewhat lower and ranges between 15% and 73%. In the subgroup of patients with diarrhoea and peripheral neuropathy, however, all patients showed impaired exocrine function with amylase and bicarbonate secretion amounting to about 40% of healthy controls in response to endogenous and exogenous stimulation.

Most of the studies performed so far have been limited to small numbers of patients due to relatively time and cost consuming tests of pancreatic functions and/or invasive methods. Although a significantly increased prevalence of pancreatic exocrine insufficiency in diabetic patients was observed in all studies, this difference may also have been biased by selection of patients that were more prone to diabetic complications, including pancreatic dysfunction. Only a few studies have used unselected patients of diabetes mellitus registries. These studies suggest relatively low frequencies of impaired pancreatic exocrine function in IDDM (26%) and NIDDM (12%). However, faecal elastase-1 measurements as used in these studies are less sensitive compared with direct and invasive pancreatic function testing.

The pathophysiological mechanisms leading to pancreatic exocrine insufficiency in diabetes mellitus are not fully elucidated. The disturbance of acinar-islet interactions with imbalance of stimulatory (insulin) and inhibitory (glucagon, somatostatin) islet hormones (fig 17) is probably one of the main reasons for pancreatic exocrine dysfunction but does not explain it sufficiently. Further pathomechanisms include pancreatic fibrosis due to angiopathy, autoimmune mechanisms, autonomic neuropathy, and altered release of gastrointestinal regulatory mediators.

As pancreatic exocrine insufficiency is usually only mild to moderate and will not lead to clinically overt steatorrhoea in the majority of patients concerned, clinical relevance of pancreatic exocrine impairment in these patients is questionable. However, patients with diabetes mellitus frequently suffer from a wide range of abdominal symptoms which markedly contribute to impairment of quality of life. At least some of these symptoms, such as pain and diarrhoea, may be attributable in part to (compensated) pancreatic exocrine insufficiency (fig 10) and might respond to enzyme treatment. Consequently, potential beneficial effects of enzyme supplementation on abdominal symptoms in diabetes mellitus warrant clinical studies. On the other hand, potential adverse effects of enzyme supplementation on glucose homeostasis need to be monitored carefully.

3.8.1 Summary

Diabetes mellitus is associated with morphological and functional impairment of the exocrine pancreas. This appears to be more extensive in patients with IDDM in whom
prevalence of mostly mild to moderate pancreatic exocrine insufficiency ranges between about 25–80%. In NIDDM patients, the prevalence of pancreatic exocrine insufficiency is somewhat lower and ranges from 15–73%. It has to be taken in mind, however, that most of these data are derived from small groups of selected patients who are probably more prone to diabetic complications, including pancreatic exocrine dysfunction. Valid population based data on the frequency of pancreatic exocrine insufficiency in diabetes mellitus are scarce, so far. Anyway, exocrine insufficiency is usually mild to moderate and not associated with overt steatorrhoea. Thus, clinical relevance of pancreatic exocrine impairment in these patients may be questionable. However, patients with diabetes mellitus frequently suffer from a wide range of abdominal symptoms which markedly contribute to impairment of quality of life and might in part be caused by a distal shift of nutrient digestion and absorption as observed in mild to moderate pancreatic exocrine insufficiency.

3.9 CROHN’S DISEASE
Pancreatic involvement—that is, pancreatic autoantibodies or increased levels of pancreatic enzymes in plasma—has been documented in up to 40% of patients with Crohn’s disease. Increased frequency of pancreatic pathology in Crohn’s disease is partly explained by disease associated well known risk factors such as increased incidence of gall stones, duodenal involvement at the papilla of Vater, and adverse reactions to drugs, for example azathioprine. Still, there are numerous patients with alterations of pancreatic function and/or morphology without these risk factors in whom pathophysiological mechanisms are not completely understood. A high incidence of pancreatic fibrosis (15 out of 36 patients) was described in an autopsy study. Moreover, in 8.7% of Crohn’s disease patients without clinical evidence of pancreatic insufficiency, morphological alterations of the pancreatic ducts were observed by ERCP. There are few studies investigating pancreatic exocrine function in Crohn’s disease to date. Mostly mild to moderate exocrine insufficiency was observed in 5–15% of patients in response to exogenous or endogenous stimulation. In 143 Crohn’s disease patients amylase and lipase outputs in response to a Lundh test meal were decreased by 15–20% compared with healthy volunteers. Enzyme secretion was not associated with duration of the disease, age, nutritional status, medication, or previous bowel surgery, but patients with ileal disease and mild activity had higher secretion rates compared with other locations and higher disease activity. Similarly, in our own recent study, duodenal perfusion with essential amino acids increased protease secretion in healthy subjects three to fourfold compared with interdigestive values. By contrast, protease secretion did not increase in Crohn’s disease patients, neither in response to this moderate endogenous stimulus nor in response to exogenous stimulation by a modified secretin cerulein test. Additionally, integration between pancreatic secretory and intestinal motor functions was disturbed. Endogenous stimulation caused exaggerated release of GLP-1 and PYY in patients with inflammatory bowel disease compared with healthy volunteers. This may in part explain reduced response to duodenal amino acids because both of these gastrointestinal hormones were shown to inhibit pancreatic exocrine secretion.

Mild to moderate exocrine insufficiency as observed in most patients affected would not be expected to cause clinical symptoms—that is, no steatorrhoea in subjects with an otherwise healthy digestive system. It might be speculated, however, that in Crohn’s disease patients with reduced absorptive capacity due to small intestinal resections, extensive inflammation, or scars and/or motility disturbances, lesser degrees of pancreatic insufficiency might suffice to induce symptoms. Accordingly, selected patients might benefit from enzyme supplementation.

3.9.1 Summary
Altogether, some signs of pancreatic pathology are observed in up to 40% of patients with Crohn’s disease and decreased pancreatic exocrine function as assessed by routine pancreatic function tests occurs in 5–15%. Moreover, patients with Crohn’s disease as a group show a decreased enzyme response to endogenous stimulation compared with healthy controls. Apart from disease associated risk factors for pancreatic disease such as increased incidence of gall stones, duodenal involvement at the papilla of Vater, and adverse reactions to drugs, impairment of pancreatic exocrine function may be a consequence of direct pancreatic affection. Moreover, disturbed regulation of pancreatic secretion in particular, and disturbed integration among gastrointestinal secretory and motor functions in general may explain
decreased digestive enzyme and bicarbonate output. In patients with reduced absorptive capacity lesser degrees of pancreatic insufficiency than usually expected might suffice to induce symptoms.

3.10 Zollinger-Ellison syndrome

Zollinger-Ellison syndrome is an uncommon disease and reports about pancreatic exocrine insufficiency in these patients are rare. Still, it is of major pathophysiological interest because a distinct mechanism causes intraluminal lack of pancreatic enzyme activity: 5–10% of Zollinger-Ellison syndrome’s patients have been reported to present with diarrhoea and steatorrhoea. This is in part due to gastric induced high volume secretion as well as mucosal inflammation, partial villus atrophy, and bile salt precipitation caused by exposure to excessive amounts of gastric acid. Moreover, low duodenal pH induces acidic destruction of pancreatic enzymes within the intestinal lumen despite normal secretory capacity (fig 8).

This, in turn means that a large volume of acid duodenal juice during investigations of suspected pancreatic steatorrhoea may indicate Zollinger-Ellison syndrome.

4.0 CLINICAL CONSEQUENCES

4.1 The physiological goal

In states of disturbed, that is, mainly diminished pancreatic exocrine function, an ideal therapy would achieve complete restoration of quantity, composition, and availability of luminal enzymatic activity. The healthy human pancreas adopts its exocrine secretory response to the size, nutrient composition, and physical properties of a meal. As a prerequisite there is a complex regulatory interplay among nutrient delivery to the duodenum and pancreatic exocrine secretion. Ingestion of an “ordinary” meal induces a transient phase of maximal enzyme output resulting in a three to sixfold increase above interdigestive outputs of all major enzymes. This is followed by a three to fourfold increase in enzyme output which is sustained for several hours; degree and duration of the digestive enzyme response are higher and longer, respectively, in response to high caloric and solid meals compared with liquid meals with low caloric content. Moreover, different macromolecules have varying stimulatory potency—lipids are the strongest stimulants followed by proteins and carbohydrates.

During small intestinal transit, enzymatic activities of all major pancreatic hydrolases decrease but at greatly different rates: lipase activity is most susceptible to destruction, and only about 20% or less of duodenal lipase may reach the terminal ileum in active form compared with about 70% of amylase.

Thus, the available evidence suggests that for perfectly mimicking physiological conditions a pancreatic enzyme preparation would need to:

- be delivered to the duodenum together with the meal;
- induce highest duodenal enzyme delivery during the first postprandial hour reaching 3000 U/min of lipase, 500 U/min of amylase, and 200 U/min of trypsin;
- thereafter, allow stable duodenal enzyme delivery at lower rates for more than two hours;
- show a decrease in enzymatic activity during small intestinal transit by about 80% for lipase, 60% for proteases, and 30% for amylase.

4.2 Insufficient luminal enzyme activity

Due to the high reserve capacity of the exocrine pancreas and because other enzymatic and non-enzymatic mechanisms may at least partly substitute for the loss of pancreatic enzymes, clinically significant malabsorption is prevented at intraduodenal enzyme activities that reach only 5–10% of physiological postprandial levels.

However, under these threshold conditions, nutrient digestion and absorption is slowed temporally and shifted aborally into the distal small intestine with significant regulatory consequences for gastrointestinal motor and secretory functions.

Further, it can be assumed that abdominal symptoms in a subgroup of patients with pancreatic insufficiency arise at least in part from these regulatory dysfunctions. This explains the favourable symptomatic response of some patients to enzyme treatment for pain, even in the absence of steatorrhoea. In conclusion, pancreatin supplementation may not only be indicated in patients with overt malabsorption due to severe pancreatic exocrine insufficiency but may also be of therapeutic value in a subset of patients with milder forms of pancreatic exocrine insufficiency.

4.3 Indications for enzyme supplementation therapy

Chronic pancreatitis is the most frequent and relevant indication for pancreatic supplementation therapy. In an unselected group of patients with chronic pancreatitis 80–90% show some degree of pancreatic exocrine insufficiency but in most patients, severe pancreatic exocrine insufficiency with overt steatorrhoea is a late event in the course of the disease. Once overt malabsorption has occurred, patients definitely need pancreatic enzyme supplementation therapy. However, it has to be taken in mind that in a fundamental study about 30 years ago DiMango et al observed duodenal lipase delivery of only about 1% of normal even with clinically established doses of pancreatin (28 KU of lipase per meal). Correspondingly, lipid malabsorption could not be normalised in these patients. These studies were performed with unprotected pancreatin and modern acid resistant microsphere preparations probably achieve considerably higher intraluminal enzyme activities. Still, even today, refractory steatorrhoea despite high doses of pancreatin is a frequent problem in enzyme supplementation therapy.

As discussed above, a therapeutic trial may also be indicated in chronic pancreatitis patients without overt malabsorption but with abdominal symptoms which cannot be attributed to the inflammatory process itself but may be due to regulatory disturbances.

During the first few weeks following onset of acute pancreatitis, pancreatic exocrine function appears to be regularly impaired and a high proportion of patients with necrotising disease may show severe exocrine insufficiency. Milder forms of pancreatic exocrine insufficiency usually recover step by step but particularly patients with expanded necrosis may need pancreatin therapy for a prolonged period of time.

Severe pancreatic exocrine dysfunction and malabsorption occur in 80–90% of patients with pancreatic cancer. Site and degree of ducal obstruction appear to be major determinants of residual pancreatic exocrine secretion in these patients. In view of the poor prognosis of these patients and the impact of nutritional status on quality of life and survival indication for pancreatin therapy should be administered generously.

Depending on the genetic background cystic fibrosis is associated with pancreatic exocrine insufficiency in the vast majority of patients. Patients presenting with steatorrhoea and/or other symptoms of malabsorption definitely need pancreatic enzyme supplementation therapy. Pancreatin supplementation has been shown to markedly improve nutrient digestion and absorption though it is rarely normalised. This may in part be due to the fact that in cystic fibrosis further disturbances of gastrointestinal secretory and motor
functions—that is, alterations of gastrointestinal pH, motility, and transit—additionally compromise assimilation of nutrients. Administration of ultra high doses of pancreatin preparations was associated with development of fibrocolonic colonopathy and should therefore be avoided.

Pancreatic resections naturally decrease pancreatic secretory capacity and it depends on the original disease process and on the type and extent of resection whether patients develop maldigestion and malabsorption. In patients with previously normal pancreatic function, even a 90–95% resection of the pancreas is generally tolerated without clinical signs of severe pancreatic exocrine insufficiency. By contrast, in patients with pre-existing chronic pancreatitis, the percentage of patients with steatorrhea is markedly increased by less extensive distal resections. Thus, pancreatic exocrine function needs to be monitored carefully postoperatively, particularly in patients who are at increased risk of developing severe pancreatic exocrine insufficiency. Naturally, high doses of pancreatin with every meal are needed following total pancreatectomy. Moreover, all patients with overt malabsorption following limited pancreatic resections need enzyme therapy.

Partial or total gastrectomy and short bowel syndrome may also be associated with intraluminal lack of pancreatic enzymes postprandially, mainly because of postcibal asynchrony—that is, dissociation between intestinal delivery of nutrients and discharge of digestive secretions. In patients operated on because of malignant disease, extensive denuvaton of the pancreas including vagotomy contributes to pancreatic dysfunction. Thus, pancreatic exocrine function should be measured in patients with symptoms of malabsorption following gastric or extensive small bowel resections. Indirect tests may be preferred because they reflect digestive action of endogenous enzymes under the patient’s pathological conditions. Pancreatin supplementation therapy should be initiated in those patients with documented exocrine insufficiency.

Mostly mild to moderate pancreatic exocrine insufficiency is observed in up to 40% of patients with coeliac disease. Impairment of pancreatic exocrine function is mainly due to decreased release of stimulatory mediators by the diseased upper intestinal mucosa and to postcibal asynchrony of secretory and motor functions. Still, in a subset of patients, the pancreas itself may also be affected. At least in children with coeliac disease, low faecal enzyme concentrations might be used to select patients who would probably benefit from enzyme treatment during the first few weeks of dietary therapy.

Diabetes mellitus is associated with morphological and functional impairment of the exocrine pancreas. Mostly mild to moderate pancreatic exocrine insufficiency is observed in about 25–80% of patients with IDDM and in 15–73% with NIDDM. Severe pancreatic exocrine insufficiency associated with overt steatorrhea which obviously necessitates enzyme therapy affects only a minority of these patients. However, patients with diabetes mellitus frequently suffer from a wide range of abdominal symptoms which markedly contribute to impairment of quality of life and might in part be caused by a distal shift of nutrient digestion and absorption as observed in mild to moderate pancreatic exocrine insufficiency.294 In such patients, a therapeutic trial with enzyme preparations may be justified but necessitates close control of blood glucose.

In Crohn’s disease decreased pancreatic exocrine insufficiency as assessed by routine pancreatic function tests occurs in 5–15% of patients. Mostly, mild to moderate exocrine insufficiency is observed which would not be expected to cause clinical symptoms—that is, no steatorrhea in subjects with an otherwise healthy digestive system. It might be speculated, however, that in Crohn’s disease patients with reduced absorptive capacity due to small intestinal resections, extensive inflammation, or scars and/or motility disturbances, lesser degrees of pancreatic insufficiency might be enough to induce overt malabsorption. Accordingly, selected patients might benefit from enzyme supplementation. Moreover, a distal shift of nutrient digestion and absorption and consecutive regulatory disturbances may contribute to symptoms and might respond to enzyme treatment.

In Zollinger-Ellison syndrome intraluminal enzymes are destroyed by excessive amounts of gastric acid which leads to steatorrhea in about 5–10% of patients. Thus, these patients need high doses of proton pump inhibitors and/or surgical therapy but usually do not benefit from enzyme supplementation.

### 4.4 Therapeutic standards

Modern pancreatic enzyme preparations consist of pH sensitive pancreatin microspheres. In order to reduce steatorrhea to less than 15 g of fat per day, a minimal dose of 25 000–50 000 IU of lipase per meal is required. In order to ensure release of enzymes throughout the digestive period it is recommended that for small meals or snacks, one tablet/capsule should be swallowed with the start of the meal, and that for major meals a second dosage should be administered during the meal.347

Acid resistant coating of the microspheres protects exogenous enzymes from acidic denaturation in the stomach but allows disintegration and release of enzymes at about pH 5.5–6 which is achieved physiologically in the postprandial period. The small size of microspheres was chosen to enable simultaneous delivery of enzymes and meal nutrients to the duodenum because larger indigestible particles (exceeding about 2 mm in diameter) are retained within the stomach until the end of the digestive period. Microsphere preparations have been shown to be superior to equivalent doses of unprotected pancreatin powder and to acid resistant monolithic capsules or tablets. However, due to the physicochemical properties of the coating the microspheres may be somewhat retained in the stomach postprandially (in the lipolytic phase of the meal)348 and—more importantly—release of enzymes within the intestinal lumen does not occur instantly but is retarded particularly if intestinal pH is below the pH threshold cited above due to loss of bicarbonate secretion.349 Thus, nutrient digestion and absorption are shifted from the duodenum to the more distal small intestine. These appear to be the main reasons why lipid digestion and absorption cannot be normalised in a subset of patients with severe pancreatic exocrine insufficiency despite administration of high doses of modern enzyme preparations.

Following (total) gastrectomy and in patients with gastric acid suppression therapy due to other reasons, unprotected pancreatin powder should be preferred. On the other hand, application of proton pump inhibitors together with pancreatin powder may increase fat absorption in patients who do not respond adequately to standard enzyme treatment.

Moreover, failure of enzyme therapy to adequately improve steatorrhea and other symptoms of exocrine insufficiency may be due to low patient compliance, intestinal infections or other disorders associated with malabsorption. These require specific diagnostic work up and therapeutic intervention.349

### 4.5 Future developments

Lipid malabsorption is regarded as the clinically most important malfunction in pancreatic exocrine insufficiency. Thus, investigations to optimise enzyme treatment have concentrated on supplementation of adequate amounts of lipolytic activity to the proximal small intestine.350
At present, administration of bacterial lipase, for example from *Barkholderia plantarii*, may be the most promising approach. This bacterial lipase has a high specific activity, is resistant to gastric acid and proteolytic enzymes, is not inhibited by bile acids, and is (at least in animal experiments) superior compared with porcine pancreatic in correcting fat malabsorption.\(^1\) On the other hand, no human data—either experimental or clinical studies—are available to date. Moreover, the human pancreatic lipase gene has been successfully transfected and expressed in vitro and in vivo. Significant production of human lipase was observed under all these conditions.\(^1\) These experiments suggest the possibility of future ectopic expression of human pancreatic lipase in the hepatobiliary system of patients with pancreatic exocrine insufficiency. Furthermore, administration of bioengineered, acid resistant human gastric lipase may offer treatment alternatives.

The primary goal of new developments is to achieve sufficient lipase activities within the upper small intestine in order to prevent lipid maldigestion and malabsorption. Thus, the galenic properties of optimised treatment alternatives should not only ensure high intraduodenal enzyme activities early postprandially but also a stable duodenal enzyme delivery for more than two hours. On the other hand, filtering colopathy in cystic fibrosis patients treated with ultra high doses of pancreatin has been attributed to the exposure of the colon to high protease activities. It has remained controversial whether the enzyme content truly played a decisive pathogenetic role in these patients. Still, it cannot be excluded that the physiological decrease in enzymatic activity during small intestinal transit may be protective for the distal intestine.

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