Uses and abuses of enzyme therapy in cystic fibrosis

Peter Durie MD FRCPC Daina Kalnins RD CNSD Lynda Ellis RN

J R Soc Med 1998;**91**:(Suppl. 34):2–13 SECTION OF PAEDIATRICS, 25 NOVEMBER 1997

Patients with cystic fibrosis (CF), who have signs and symptoms of maldigestion due to pancreatic insufficiency, will require pancreatic enzyme therapy with meals and snacks. Often the diagnosis of CF is established as a direct or indirect result of pancreatic failure. Almost 50% of patients are diagnosed before the age of 1 year and 85% before the age of 5 years. Failure to thrive, frequent loose or bulky stools, rectal prolapse or the triad of hypoalbuminaemia, oedema and anaemia in an infant should suggest the diagnosis. Frequently, however, signs and symptoms of CF are quite subtle: at clinical presentation the phenotypic stereotype of a clinically wasted child with a protuberant abdomen, ravenous appetite, persistent cough and loose frequent stools applies to a relatively small number of patients. Approximately 15% of patients possess sufficient exocrine pancreatic function to absorb nutrients normally[1]. Although 'pancreatic sufficient' patients are often said to have *normal* pancreatic function, quantitative assessment by sophisticated intubation studies demonstrate that the majority possess impaired pancreatic ductal (fluid and electrolyte) and acinar (enzyme) secretion[2,3]. These studies also confirm the large reserve capacity of the exocrine pancreas: steatorrhoea due to pancreatic insufficiency is present when patients lose more than 98–99% of residual exocrine pancreatic function. Patients with pancreatic sufficiency possess enzyme secretion ranging from the lower limits of the reference range to values marginally above the threshold for developing steatorrhoea.

Following introduction of neonatal screening programmes, it has become apparent that a considerably higher percentage of pre-symptomatic infants with CF are pancreatic sufficient in early infancy[4]. However, pancreatic insufficiency develops in most of these patients within the first few years of life.

CLINICAL TESTS OF PANCREATIC FUNCTION

Exocrine pancreatic function is difficult to assess because the pancreas and its secretions are anatomically inaccessible[5]. There is no such thing as an 'ideal' pancreatic function test capable of satisfying the criteria listed below:

- Economic
- Simple to perform
- Non-invasive
- Specific
- Quantitative
- Reproducible

Nevertheless, provided the limitations of existing clinical tests are understood, they can be of considerable help in the initial assessment and ongoing care of patients with CF. Pancreatic function tests may be categorized into three general groups (Table 1).

Direct tests

Direct tests are used to measure pancreatic secretions, either following stimulation of the pancreas using exogenous hormonal secretogogues (secretin, cholecystokinin, etc.) or by endogenous nutrients (Lundh meal, fatty acids, amino acids, etc.). All direct tests are invasive since they necessitate nasointestinal intubation. Successful evaluation of pancreatic secretions is contingent upon stimulating both acinar and ductal secretions, excluding gastric secretions and quantitatively aspirating pancreatic secretions[3,6]. Unfortunately, no standard methodology has been established. Investigators use a variety of exogenous hormones given singly, together or sequentially. Others use intraluminal nutrients to stimulate pancreatic secretion[7]. While the latter tests are more physiologic, they suffer from a variety of technical limitations. Intestinal perfusion with a non-absorbable marker is recommended to accurately quantify pancreatic secretions[3,6]. This is accomplished with a double lumen tube, such that the proximal port opens opposite the ampulla of Vater for infusing the non-absorbable marker, and a distal port near the ligament of Treitz can be used to aspirate pancreatic juice mixed with the infused marker solution. A nasogastric tube is placed to aspirate gastric contents and to monitor for reflux of intestinal secretions into the stomach.

If performed correctly, direct pancreatic function tests are highly specific and capable of evaluating the entire range of pancreatic function[3]. Direct tests are of great value for

Division of Gastroenterology and Nutrition, the Research Institute and the Department of Dietetics, The Hospital for Sick Children and the Department of Pediatrics, University of Toronto, Toronto, Ontario, Canada

Correspondence to: Dr Peter R Durie, Department of Gastroenterology and Nutrition, Hospital for Sick Children, 555 University Avenue, Toronto, Ontario M5G 1X8, Canada

Table 1 **Tests of exocrine pancreatic function**

Direct tests	*Indirect tests*	*Blood tests*
Exogenous stimulants	Stool	Isoamylase
Secretin	Microscopy—fat, meat fibres	Lipase
Cholecystokinin*	Steatocrit	Cationic/anionic trypsinogen
Caerulein*	Faecal balance studies	Pancreatic polypetide
Bombesin*	Trypsin, chymotrypsin	
	Elastase	
Nutrient stimulants		
Lundh meal	Breath tests	
Fatty acids	Carbon-14-lipid substrates	
Amino acids	Carbon-13-lipid substrates	
	Starch	
	Urinary/plasma markers	
	Bentiromide	
	Fluorescein dilaurate (pancreolauryl)	
	Dual-labelled Schilling test	
	Urinary lactulose	

*Used in various dose combinations with or without secretin

assessing pancreatic reserve in patients with pancreatic sufficiency and for identifying defects of pancreatic fluid and anion secretion in patients with an uncertain diagnosis of CF. Unfortunately, these invasive, time consuming and complex tests, which require special skills to perform and interpret, have a very limited role for routine clinical assessment of exocrine pancreatic function.

Indirect tests

These tests detect secondary abnormalities of pancreatic dysfunction[5]. Some measure faecal products of maldigestion (*see* Table 1), while others depend on the ability of pancreatic enzymes to cleave ingested synthetic substances generating absorbable end-products that are detectable in breath, blood or urine. Many indirect tests, such as faecal fat, lack specificity and are unable to differentiate between pancreatic, biliary or intestinal causes of nutrient malabsorption. They cannot reliably quantitate exocrine pancreative reserve in patients with pancreatic sufficiency. Most tests are relatively non-invasive, however, and once the diagnosis of CF is firmly established may be used to determine the need for pancreatic enzyme therapy. Qualitative tests such as microscopic examination of the stool[8], or steatocrit[9], provide limited information since they fail to account for faecal losses of nutrients in relation to intake. Carefully performed faecal balance studies remain the most useful clinical tool for establishing a diagnosis of pancreatic insufficiency and for monitoring response to enzyme therapy. Seventy-two hour stool collections can be performed at home, with a high degree of accuracy, provided the parent or caregiver receives appropriate instructions. All major nutrient classes (fat, protein and carbohydrate) and total energy content may be measured[5,10]. Faecal fat is the most commonly used clinical test[11]. It is absolutely essential to quantitate nutrient intake and express faecal nutrient losses as a percentage of intake. As shown in Figure 1, there is considerable intra-patient variability in fat intake, even among CF patients of the same age. Thus, sole reliance on measurement of faecal fat without knowledge of fat intake will not accurately identify patients with pancreatic insufficiency nor determine the severity of fat maldigestion. Despite previous claims of its usefulness[12], faecal weight is not a particularly accurate way of assessing pancreatic function status. Figure 2 shows a high degree of correlation between faecal weight and other more quantitative measures of faecal content such as faecal energy (kcal/day) or faecal fat (g/day). However, the weak correlation between faecal weight and faecal losses expressed as a percentage of nutrient intake (faecal energy or fat), limits its clinical utility. The poor relationship is almost certainly explained by the wide intrapatient variability in nutrient intake.

Faecal balance studies do not discriminate between patients with pancreatic maldigestion from those with other causes of malabsorption due to intestinal or hepatobiliary disease. Nevertheless, in a patient with a confirmed diagnosis of CF, evidence of nutrient maldigestion is almost certainly due to pancreatic insufficiency. In addition, faecal balance studies provide baseline information prior to instituting therapy, are useful for monitoring the pancreatic function status of pancreatic sufficient patients, and for

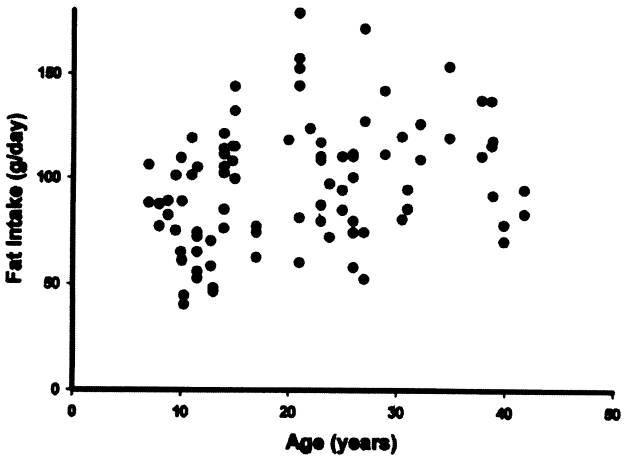
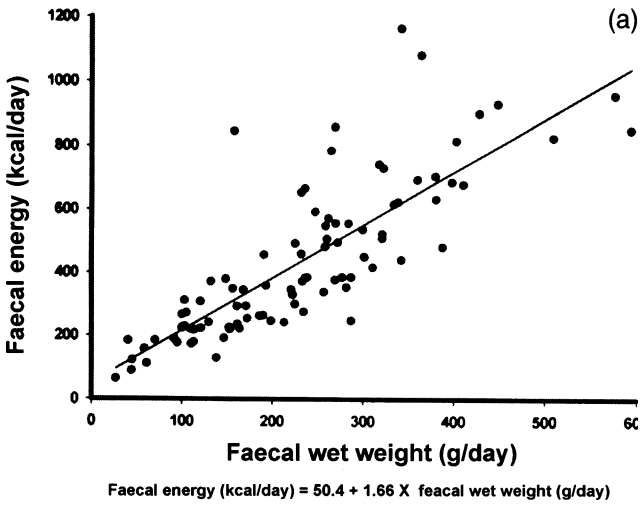


Figure 1 **Mean fat intake (g/day) plotted in relation to age (years) in 43 patients with cystic fibrosis and pancreatic insufficiency (mean age 21.2 years, range 7.0 to 41.9 years).** A total of 94 observations were made. Average daily fat intake was calculated using a computerized system. The patients weighed and recorded intake of all nutrients over a 72-h period while eating a normal diet at home. There was considerable variability in fat intake between patients, even among those of the same age. $r = 0.30$; $P < 0.004$



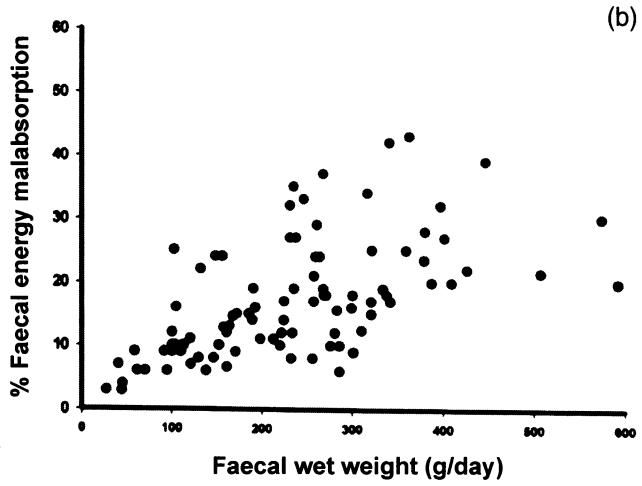


Figure 2 **Faecal weight, faecal fat and faecal energy were analysed in 43 patients with cystic fibrosis and pancreatic insufficiency (age 21 years, range 7–42 years) while patients were receiving pancreatic enzyme supplements.** A total of 94 observations were made. (*a*) There was a strong correlation between faecal energy (kcal/day) and faecal wet weight (g/day). (*a*) Identical results were obtained when faecal fat (g/day) was correlated with faecal wet weight (g/day) (data not shown). However, (*b*) faecal energy, expressed as a percentage of energy intake (% malabsorption), showed a weak correlation with faecal wet weight (g/day). This poor relationship, which is explained by wide intrapatient variability in nutrient intake (*see* Figure 1), limits the clinical utility of faecal weight measurements as a marker of nutrient maldigestion. Similar results were obtained when faecal fat, expressed as percentage of fat intake, was correlated with faecal wet weight (data not shown). (*a*) $r = 0.81$; $P = 0.0001$. (*b*) $r = 0.60$; $P = 0.0001$

assessing the efficacy of pancreatic enzyme supplementation in those with documented pancreatic failure.

Pancreatic enzymes such as trypsin or chymotrypsin may be measured in faeces using highly specific synthetic substrates. Faecal chymotrypsin is more reliable than faecal trypsin because the latter enzyme is susceptible to proteolytic degradation by pancreatic enzymes and colonic bacteria[13,14]. Faecal enzyme tests are relatively specific but are insensitive. Recently, an enzyme-linked immunosorbent assay has been developed capable of measuring human pancreatic elastase in faeces[15,16]. This particular test can be performed when patients are receiving pancreatic enzyme supplements because it does not cross react with porcine elastase. None of the faecal enzyme tests are of value for evaluating response to enzyme therapy, but faecal chymotrypsin assay is useful to assess patients for compliance.

Breath tests rely on the principle that specific by-products of maldigestion may be emitted in exhaled breath[5,17]. These tests have no clear defined clinical use but may have applicability to research studies. The simplest breath test relies upon hydrogen-producing colonic bacteria to degrade undigested starch, releasing hydrogen[17] or $^{13}CO_2$ in breath[18]. Several breath tests, which have been developed using a variety lipid substrates and/or fatty acids constituted with a stable isotope ($^{13}CO_2$), rely upon expired $^{13}CO_2$ concentration as an index of the efficacy of digestion[19,20]. Breath tests are non-invasive and simple to perform but are relatively qualitative.

Other indirect tests involve administering a substrate by mouth and measuring a cleaved product of digestion in urine or plasma[5]. Bentiromide is the most commonly used clinical test of this type. The pancreolauryl test relies on the same general principles with a different substrate. Bentiromide indirectly evaluates pancreatic chymotrypsin

activity[21]. A synthetic compound (N-benzoyl-L-tyrosyl-para-aminobenzoic acid) is cleaved by pancreatic chymotrypsin within the intestinal lumen releasing the marker para-aminobenzoic acid (PABA). PABA is readily absorbed, conjugated in the liver and excreted in the urine. In the conventional test, a 6-h urine collection is performed and the urinary excretion of ingested PABA is determined[22]. In patients with CF, PABA measured in plasma is more reliable and avoids the difficulty of a lengthy urine collection[23,24]. Bentiromide can only identify patients with marked loss of pancreatic function. Falsely abnormal tests, have been reported in patients with intestinal, hepatic or renal disease due to abnormalities of absorption, conjugation or excretion of PABA. To correct for these abnormalities, a two-stage test has been proposed by first giving bentiromide then an equivalent dose of free PABA. Alternatively, Bentiromide may be given together with another substance such as para-aminosalisylic acid. Unfortunately, bentiromide is no longer commercially available in most countries.

Blood tests

Immunoassays have been developed which are capable of measuring nanogram quantities of pancreatic enzymes or pancreatic hormones in the circulation (*see* Table 1). In CF, immunoassays for pancreatic trypsinogen and lipase have been most extensively evaluated[25–27]. These tests rely upon the assumption that the level of circulating enzyme and/or hormone reflect exocrine pancreatic reserve. Unfortunately, due to the obstructive nature of pancreatic pathology in CF, this assumption does not hold true. It is well known that young infants with CF (pancreatic sufficient or pancreatic insufficient) have very high levels of circulating pancreatic enzymes. In fact, most newborn screening programmes take advantage of high immunoreactive trypsinogen concentrations to identify patients with CF[4]. With advancing age, CF patients with pancreatic insufficiency show declining levels of circulating enzymes which reach unmeasurable values by 7 or 8 years[25–27]. This almost certainly reflects progressive acinar atrophy with replacement by fibrous tissue and fat. In contrast, patients with the pancreatic sufficient phenotype have normal and frequently high, fluctuating levels of serum trypsinogen at all ages[27]. Thus, in early infancy or childhood, the underlying pancreatic pathophysiology in CF limits the clinical value of serum enzymes for determining pancreatic status. After 7 or 8 years of age, however, the test accurately distinguishes pancreatic insufficient from pancreatic sufficient patients and may be used for monitoring the pancreatic function status of pancreatic sufficient patients.

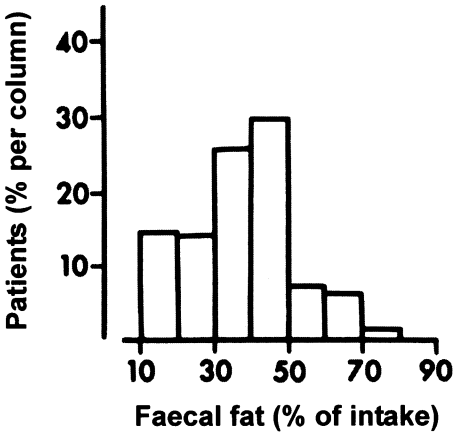


Figure 3 **The range of steatorrhoea in 190 untreated patients with cystic fibrosis.** In some patients, fat losses, expressed as a percentage of fat intake, are marginally abnormal, while others exhibit fat losses in excess of 70% of fat intake (from Forstner G *et al.* Perspective in Cystic Fibrosis. In: *Proceedings of the 8th International Congress on Cystic Fibrosis*) Mississauga, ON: Imperial Press Ltd, 1980: 137–48

PANCREATIC ENZYME SUPPLEMENTATION IN CF PATIENTS WITH PANCREATIC INSUFFICIENCY

Assessment at diagnosis and following initiation of therapy

When the diagnosis of CF is established, pancreatic function status should be objectively defined. Provided nutrient intake is quantified, a carefully performed 72-h faecal fat balance study provides reliable clinical information. At our centre, this test is performed in combination with other screening tests (e.g. serum vitamins A and E). If the patient is found to be pancreatic insufficient, baseline information is useful to evaluate response to therapy. Seventy-two hour faecal fat studies will reveal considerable variability in the severity of steatorrhoea (Figure 3). Fat losses in some patients will be marginally above the threshold for developing steatorrhoea while others will exhibit fat losses in excess of 70% of fat intake. Patients with pancreatic insufficiency show a relatively good correlation between residual pancreatic function (colipase secretion) and the severity of fat malabsorption. Additional factors almost certainly contribute to the wide variability in severity of maldigestion between patients. Information concerning the individual patients' genotype may provide additional insights concerning pancreatic function status[28,29]. (For further information on this topic see p. 40) If the diagnosis of CF is in doubt, or if the status of the exocrine pancreas remains unclear, more detailed direct pancreatic function studies should be contemplated. In our experience, the more invasive quantitative pancreatic stimulation test is of great clinical value for defining the pancreatic reserve of patients with pancreatic sufficiency.

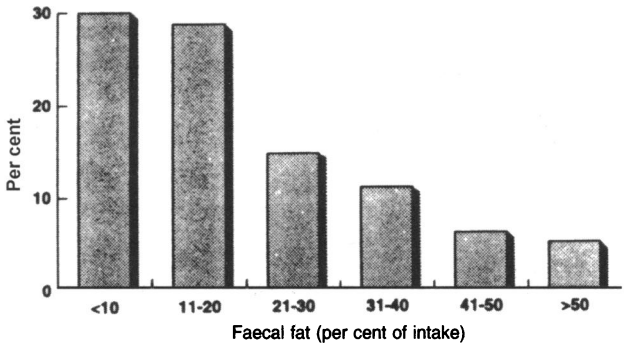


Figure 4 **The results of 240 72-h faecal fat balance studies performed in cystic fibrosis (CF) patients with pancreatic insufficiency while receiving pancreatic enzyme supplements with meals and snacks.** In general, the enzyme doses conformed to the guidelines recommended by the recent consensus committee report of the US CF Foundation and the Food and Drug Administration (Ref 30). Enzyme therapy came close to correcting nutrient maldigestion in only one-third of patients. The remaining patients exhibited moderate to severe steatorrhoea, despite seemingly adequate doses of pancreatic enzymes (from Durie PR. In: *Ninth Annual North American Cystic Fibrosis Conference 11–15 October 1995, Dallas, Texas*)

We have used 72-h fat balance studies to evaluate the response to enzyme therapy in patients suspected of persistent nutrient maldigestion. Figure 4 shows the results of 240 faecal fat balance studies performed in CF patients with pancreatic insufficiency who were receiving pancreatic enzymes in doses that the patient and/or caregiver considered to be appropriate. Enzyme doses generally conformed to the guidelines recommended by the recently published consensus committee report of the US CF Foundation and the Food and Drug Administration[30]. It should be emphasized that the patients we studied are not representative of the entire clinic population, because clinical evaluation was limited to those with subjective evidence of a poor response to enzyme therapy, such as abdominal bloating and/or pain, bulky malodorous stools and/or evidence of growth failure. In this patient cohort, enzyme therapy came close to correcting nutrient maldigestion (faecal fat losses less than 10% of intake) in only one-third of patients; in another third, fat losses were moderately severe (11–20% of intake), while fat losses were considerably higher, ranging from 20% to more than 70% of fat intake, in the remaining third.

None of the current enzyme preparations achieve the ideal clinical objectives of therapy which are to :

- Correct macronutrient maldigestion
- Correct micronutrient maldigestion
- Eliminate abdominal symptoms attributable to maldigestion
- Sustain normal growth and nutritional status on a normal diet

In comparison to patients with pancreatic insufficiency due to other aetiologies, CF patients are particularly difficult to treat. A variety of related and unrelated factors, which are listed in Table 2, may contribute to the lack of success of enzyme therapy. Additional, poorly understood factors may contribute to the poor response of existing commercial products. Assessment of response in the individual CF patient with pancreatic insufficiency, therefore, necessitates insight into the variables that may influence efficacy. These include the pharmaceutical and biological properties of the various enzyme products, issues concerning patient compliance and a variety of host factors within the gastrointestinal tract, the pancreas and the hepatobiliary system.

Pancreatic enzyme products

Pancreatic enzyme extracts primarily of porcine origin have been used since the 1930s to treat maldigestion due to pancreatic insufficiency. Marketed enzymes include conventional products and various forms of encapsulated enzymes coated by an acid resistant film. Most conventional enzyme preparations consist of desiccated porcine pancreatic extracts enclosed in gelatin capsules. The enteric coated forms vary considerably in their biochemical coating, their

Table 2 **Pancreatic enzyme therapy—potential confounding factors**

	Host			
Product	***Gastric***	***Intestinal***	***Pancreatic***	***Hepato/biliary***
Dose	Inactivation	Intestinal pH	Bicarbonate	Cystic fibrosis liver disease
Potency	Mixing	Motility	Enzyme secretion	Bile acid deficiency
Formulation	Emptying	Resection		Bile acid precipitation
Compliance	Acid hypersecretion	Bacterial overgrowth		
Timing		Mucosal hydration		

biophysical dissolution properties and the size of the microspheres or microtablets.

CF caregivers have considered pancreatic enzyme supplements to be quite safe and well tolerated. Nevertheless, significant side effects have been noted, including mouth and perianal irritation, intestinal allergic reactions, and in rare cases, severe, sometimes fatal anaphylactic reactions following inhalation of the powdered form of enzyme[31]. Hyperuricosuria and hyperuricaemia are recognized complications of enzyme replacement therapy, due to the high purine load following high oral doses of pancrealipase[32,33]. In 1994, Smyth *et al.*[34] first described a severe colonic complication, which has been attributed to ingestion of large doses of potent enteric coated enzyme supplements. This severe and unusual form of colonic submucosal fibrosis, termed fibrosing colonopathy, may affect focal portions of the colon or can be pancolonic in extent. Although the precise aetiology of fibrosing colonopathy remains to be determined, case–control studies performed in the UK[35] and the USA[36] show a strong statistical association between the risk of fibrosing colonopathy and total daily enzyme dose. As will be discussed below, the doses that were used, which greatly exceeded the calculated needs of patients, appear to have been prescribed on the basis of several erroneous assumptions.

Commercially available enzyme products (even those marketed by the same manufacturer) may vary in terms of potency and pharmaceutical properties. The relative potencies of individual products are not easily comparable even from the same pharmaceutical company. As shown in Table 3, various strengths of enteric coated products from the same manufacturers are not comparable (e.g. Pancrease MT4 and MT20 have 4000 and 10 000 units of lipase, respectively) making it difficult to calculate equivalent doses if capsules are being substituted. Similarly, the relative proportions of proteolytic, lipolytic and amyolytic activities vary from product to product. Theoretically, a product with more lipase (and colipase) in relation to protease will be more efficacious, because pancreatic proteases, especially chymotrypsin, readily denature pancreatic lipase within the intestinal lumen[37,38].

It should be emphasized that pancreatic enzymes are relatively crude biological extracts which contain numerous impurities and other proteins. There is a fair degree of batch to batch variation in enzyme activity. Enzymes are susceptible to loss of activity with time and this process is accelerated by exposure to sunlight, heat or high humidity. National regulatory agencies mandate that manufacturers provide information concerning the *minimum* activity for lipase, protease and amylase during the shelf life of the product. This information is based upon crude standardized enzymatic assays which provide very little information concerning the enzymatic activities of more than 25 individual enzymes contained in pancreatic extracts. Actual enzyme activity, particularly for lipase and proteases, often greatly exceeds the stated activity[39,40]. In some cases actual enzyme activity exceed stated activity by almost 200% (Table 4).

Table 3 **Lipase activity (U/capsule) of commercial pancreatic enzyme products***

	Pancrease MT	*Creon*	*Organon ECS*
Conventional	—	—	8 000
Enteric coated	4 000	8 000	8 000
	10 000	25 000	20 000
	16 000		

*Sold in Canada (1995)

Table 4 **Pancreatic enzyme therapy—actual versus stated enzyme activity (%)**

	Lipase (%)	*Protease (%)*
Creon 8000	133	190
Pancrease 4000	155	135
Pancrease 16000	150	160
Ultrase 24000	124	125

Modified from Kraisinger *et al.* (Ref 39)

Conventional enzymes

Previous studies by Graham *et al.*[41] demonstrated that the lipase activity of several older commercially available products was extremely variable and some products were particularly low in lipase activity. The majority of conventional products (i.e. capsules containing pancrealipase powder) are no longer marketed due to the fact that most caregivers have expressed a preference for the enteric coated forms. Despite their limitations, we remain convinced that conventional enzymes continue to have a clinical role in the treatment of pancreatic dysfunction.

In the 1960s, studies performed at the Mayo Clinic conclusively demonstrated major obstacles to the effective delivery of orally administered conventional pancreatic enzymes to the small intestine[42]. In effect, ingested, unprotected pancreatic enzymes are denatured in the harsh gastric environment, prior to entry to the small intestine. Pancreatic lipase is much more susceptible to acid-peptic destruction than most proteases. Thus, although enzyme therapy with conventional enzymes were shown to improve nutrient digestion due to pancreatic insufficiency, it was believed that the lack of efficacy was due to inadequate

delivery of active enzyme to the proximal small intestine. Nevertheless, studies of patients with chronic pancreatitis demonstrate that maldigestion is not corrected even when pancrealipase is delivered directly to the duodenum[43].

Direct pancreatic function studies of adult patients with chronic pancreatitis or CF suggest that approximately 28 000–30 000 units of lipase must be delivered to the proximal intestine to eliminate steatorrhoea[3,6]. This estimate, which is based upon the observation that between 3–10% of mean stimulated endogenous pancreatic lipase is required to prevent steatorrhoea, assumes the intraluminal environment of the CF intestine is the same as in health. Although this assumption is almost certainly incorrect, simply increasing the dose of enzyme is unlikely to correct the problem of maldigestion. Patients with pancreatic insufficiency tend to have gastric acid hypersecretion and due to pancreatic pathology, there is a relative deficiency of bicarbonate secretion from the pancreaticobiliary tree. Thus, patients with pancreatic insufficiency are likely to possess a more acidic proximal intestine than healthy subjects[44]. In health, a cyclic adenosine monophosphate (cAMP)-mediated chloride channel, the CF conductance regulator protein (CFTR) is expressed on the apical surface of epithelial cells lining the small pancreatic and biliary ducts. Secretin mediates cAMP induced chloride secretion, and chloride–bicarbonate exchange induces secretion of an alkaline rich fluid which enters the duodenum. In CF, due to the absence of CFTR (or its dysfunction), both chloride and bicarbonate secretion is deficient[2]. This secretory defect leads to reduced fluid secretions and a further impairment in the ability of pancreaticobiliary secretions to neutralize the acid load entering the proximal small intestine. Similar mechanisms appear to mediate bicarbonate secretion within the proximal small intestine. Consequently, the intraluminal environment is often well below the optimal pH for maximal pancreatic enzyme activity, and may hasten inactivation of enzymes (particularly lipase) within the small intestine[44,45].

In the early 1980s, several studies evaluated the effects of neutralizing or suppressing gastric activity in the hope of improving the chances of delivering enzymes intact to the upper intestine. A variety of antacids and inhibitors of gastric acid secretion have been evaluated. Graham noted that the type of antacid was important[46]. Sodium bicarbonate appeared to be efficacious, whereas antacids containing calcium, aluminium or magnesium exacerbated fat maldigestion due to the formation of fatty acid soaps which have limited solubility in the intestine. Studies performed in patients with CF revealed somewhat mixed results with either antacids or histamine antagonists[47–50], but comparisons are problematic, due to a great degree of variability, from study to study, in the dose of pancreatic enzymes and/or adjuvant designed to raise gastric pH. Durie *et al.*[47] demonstrated that CF patients given enough pancreatic enzymes with either sodium bicarbonate (15 g/meal/day) or cimetidine (20 mg/k/day) had significantly reduced steatorrhoea in comparison with those given conventional enzymes alone. Similar results were observed by Boyle *et al.*[48] and Cox *et al.*[49] in CF patients given 300 mg of cimetidine before meals. In contrast, Schoni *et al.*[50] observed no improvement in steatorrhoea with cimetidine but the dose or the type of enzyme given was not specified.

Enteric coated microspheres

Since the early 1980s, a variety of enteric coated preparations have been used as the enzyme of choice in the treatment of pancreatic insufficiency[51]. Some of the first attempts to protect the enzymes utilizing enteric coated tablets were ineffective. Due to their size, the tablets were selectively retained in the stomach and dissociated from the chyme entering the duodenum. When these tablets were crushed and repackaged into capsules, there was a concomitant improvement in fat maldigestion. Experience with other pharmaceutical products using coating of microspheres with various polymers led to the introduction of microspheres and/or microtablets of enzymes protected by a variety of acid resistant enteric coatings. It was argued that efficacy would be improved if the pancreatic enzymes were protected from the harsh acid-peptic environment of the stomach and greater quantities of active enzyme would be released into the more alkaline small intestine following dissolution of the protective coating. The general experience in the care of CF patients using the earlier enteric coated products (5000–8000 units of lipase/capsule) appeared to suggest that patients could ingest fewer capsules and therefore less enzyme as a total daily dose[52–59]. Most published studies demonstrated that enteric coated products were of equal, or slightly superior efficacy, when the daily dose of an enteric product was approximately half that of an equipotent conventional enzyme product. In reality, many patients did not reduce the number of pills they were ingesting. Furthermore, some caregivers recommended that doses be increased, making the assumption that 'more is better', or that gastrointestinal symptoms can be controlled by higher doses of enzymes. A number of erroneous assumptions, as follows, appear to have been promulgated by caregivers and communicated to their patients.

- Pancreatic enzymes are innocuous
- The dose and potency of conventional enzymes were inadequate
- All gastrointestinal symptoms in CF are due to pancreatic insufficiency

- Improved nutritional status of patients with CF can be attributed to introduction of enteric coated enzyme products
- Caregivers know what doses of enzymes their patients are taking
- Patients with persistent steatorrhoea will benefit from higher potency enzymes
- Enzymes given in higher doses will relieve gastrointestinal disease.

Consequently, when the more concentrated enzyme preparations (greater than 20 000 units lipase per capsule) were introduced in the early 1990s, there was an escalation in the total daily dose of ingested active enzymes in a number of centres. This resulted in a marked increase in global sales of pancreatic enzyme products. Regardless of the precise aetiology of fibrosing colonopathy, current epidemiological evidence shows a strong association between the daily dose of enzymes (both normal and high potency products), and the risk of this newly recognized complication[34–36].

The rapidity of dissolution of the protective enteric coating is influenced by the biochemical properties of the acid resistant coating, the size of the microsphere or microtablet (effect of surface area), the thickness of the protective coating and the intraluminal environment of the host. There is considerable *in vitro* variability in the optimal pH at which the protective coating dissolves from product to product[39]. As will be discussed below, the *in vivo* characteristics of the various products have not been adequately evaluated. For example, very little is known about the site of dissolution of the protective coating within the small intestine in health or in patients with CF.

Surprisingly, there are few carefully performed studies comparing the different formulations and little *in vivo* data that conclusively demonstrate the relative superiority of a single product. Theoretically, commercial products comprising of variably sized microspheres carry an advantage, since the stomach selectively sifts different sized particles at various stages of gastric emptying. Meyer *et al.*[60] demonstrated that the smallest spheres empty early while larger particles empty at later stages of gastric emptying. Theoretically, therefore, variable sized microspheres will be evenly distributed in chyme throughout gastric emptying. Nevertheless, products with variable sized microspheres have never been carefully evaluated in terms of efficacy of digestion in relation to microtablets.

Once the microspheres or microtablet enters the small intestine, the coating is expected to dissolve, releasing active enzyme into the intestinal lumen to facilitate digestion. In health, digestion is essentially complete within the first 150 cm of the small intestine. It is most unlikely that the enteric coating dissolutes in the duodenum or even the proximal jenunum. In alkaline pH conditions, *in vitro*, the coating takes up to 10–15 min to dissolve (Durie, unpublished). Furthermore, in patients with CF, the relatively acidic intestinal environment may delay, or even prevent dissolution of the protective enzyme coating[43–45]. Theoretically, enzymes with an enteric coating that dissolves at a slightly acidic pH might be more efficacious. If the dissolution characteristics of the product approaches pH 4.0, however, there would be a tendency for the coating to dissolute within the stomach, effectively negating the objective of the protective coating. Most commercially available products have a polymeric coating that dissolves at a pH of between 5.2 and 6.0[39]. Robinson *et al.*[45] evaluated post prandial duodenal pH in children with CF and in age-matched controls. In comparison with the controls, the patients with CF experienced significantly longer post-prandial periods when the duodenal pH was below 4, which is known to be below the dissolution pH of the coating and also will irreversibly denature pancreatic lipase. Furthermore, the duodenum of the patients with CF had significantly less time above ph 5.8 which in turn suggests that the enteric coating would take longer to dissolve. This study demonstrated a significant direct relationship between the degree of residual fat maldigestion and duodenal pH levels. Similar observations were made in a study of 24-h ambulatory gastric and duodenal pH profiles in patients with CF[44]. Duodenal pH fell in the first post prandial hour and with successive meals duodenal pH became lower. However, the total time duodenal pH remained below 5 varied considerably from patient to patient. Thus, in theory, a product with a lower optimal pH for dissolution of the coating of approximately 5.0 would be expected to be more efficacious. In a double-blind cross-over study, we compared the efficacy of two protective coatings, each with a dissolution pH of 5.2 and 6.0, respectively[60]. In all other respects the two products were identical. Seventeen patients completed two randomly assigned treatment arms; 72-h stool collection were completed at the end of each period. We were surprised to discover that there was no difference in faecal weight, faecal energy or faecal fat with the two products. Thus, the product with a coating that dissolved at a lower pH appeared to offer no clear advantage[61].

Low intestinal pH in patients with CF may influence additional components of nutrient digestion. In a series of elegant studies, Zentler-Munro *et al.*[62,63] evaluated post prandial jejunal contents in healthy adults and in adults with pancreatic insufficiency due to CF. Even in health the intraluminal contents of the jejunum was below pH of 5 for significant periods of time and during periods of low intestinal pH there was a significant reduction in bile acid concentration and lipase activity, which impaired lipolysis.

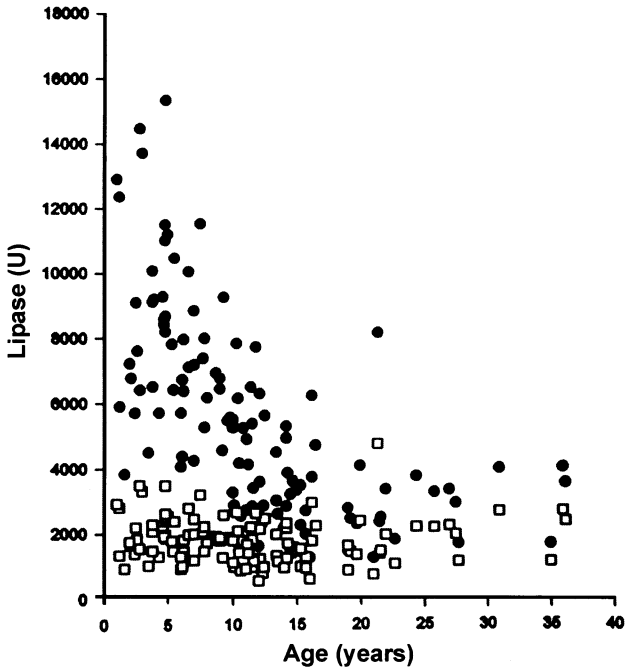


Figure 5 **Pancreatic enzyme intake (lipase units) plotted against age among treated cystic fibrosis patients with pancreatic insufficiency.** When enzyme intake was expressed as units of lipase per kilogram body weight per day (•) enzyme dosage was high in infancy and fell markedly with increasing age ($r = 0.62$, $P = 0.0001$). However, when enzyme intake was expressed as units of lipase per gram fat ingested per day (□), enzyme dose was the same at all ages ($r = -0.052$, $P = 0.58$). This result was expected, because fat intake per kilogram body weight per day is high in infancy and decreases with age

In the pancreatic insufficient patients with CF, the separate effects of bile acid precipitation and lipolysis were examined by performing sequential studies while the subjects were receiving pancreatin, cimetidine, or both together. Postprandial jejunal pH was lower than that observed in healthy subjects and bile acid precipitation was greatly increased in the CF subjects in comparison to healthy controls. Low jejunal pH, in turn, greatly reduced lipolysis and fatty acid solubilization. A combination of pancreatin and gastric acid inhibition produced less bile acid precipitation, improved lipid solubilization and increased lipolysis. Thus, the relatively acidic intestinal environment of CF patients is likely to have significant effects, not only to dissolution of the protective enzyme coating, but also on intraluminal digestion.

GUIDELINES FOR ENZYME DOSING

Published guidelines in a recent consensus statement by the US CF Foundation and the Food and Drug Administration provide a rational dosing schedule[30]. However, as outlined above, the response of individual patients can be expected to vary considerably. In addition, the maximum recommended dose, which is estimated on the basis of lipase units per kilogram body weight per meal, may be excessive for adults. It is preferable to estimate enzyme intake on the basis of nutrient intake rather than body weight. By setting a limit of 4000 units of lipase per gram fat per day beyond 1 year of age, excessive doses would be avoided. A recent survey of enzyme dosing patterns at the Hospital for Sick Children, among patients ranging in age from infancy to adulthood, showed very similar doses of enzyme when expressed as units of lipase per gram fat ingested per day (Figure 5). When expressed as units of lipase per kilogram body weight per day, however, the enzyme dosage was high in infancy and fell markedly with age. This observation was expected, because fat intake per kilogram body weight per day should decrease with age. For example, infants ingest approximately 5 g of fat per kilogram per day whereas adults ingest on average only 1–2 g of fat per kilogram per day. Thus, the exercise of calculating enzyme intake, illustrates the value of age-adjusted guidelines with ranges of enzyme doses based on body weight. Perhaps more importantly it emphasizes the value of relating doses to nutrient intake.

PRACTICAL ISSUES CONCERNING ENZYME THERAPY

Most patients are able to swallow whole capsules. Others, unable to swallow the pills should open the capsules and swallow the beads without chewing them. Infants can receive enzymes (powder or enteric coated spheres) mixed with some food item. Powdered enzymes may induce mouth bleeding and patients often suffer from buttock excoriation; therefore, proper mouth care (applying vaseline around the mouth) and buttocks care (using a zinc based cream) are required to prevent irritation from enzymes. Generally, these side effects improve with time. There are no convincing data concerning the timing of enzyme dose with a given meal or snack. For practical reasons, we recommend giving enzymes before and during meals. If patients take a particularly long period of time to complete a meal, or if the amount ingested is unpredictable, we recommend giving one-third to one-half the estimated dose at the beginning of the meal and then additional amounts half way through the meal and/or at the end of the meal.

Compliance with enzyme therapy should be reviewed routinely. One of us (DK) completed a formal survey, by questionnaire, of patient compliance with enzyme therapy. As shown in Figure 6, a significant percentage of children, and particularly teenagers, admitted to poor compliance with enzymes: in several cases poor compliance occurred with alarming frequency. The results of this survey almost certainly underestimate the extent of the problem. Thus, it should be assumed that a significant percentage of children,

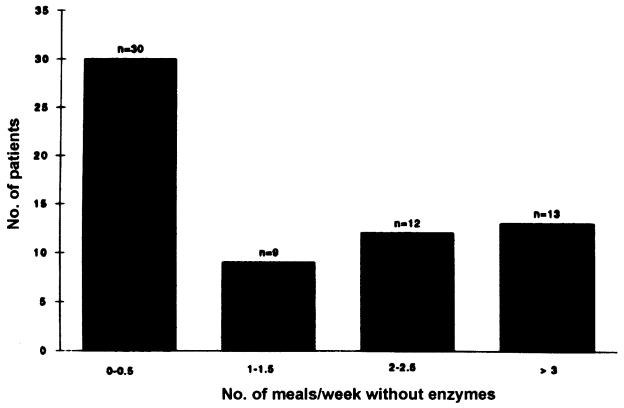


Figure 6 **The results of a formal questionnaire of compliance with enzymes are shown.** Sixty-four cystic fibrosis patients with pancreatic insufficiency (mean age 9.8 ± 4.1 years) were prospectively evaluated. Over 50% of the patients admitted to not taking enzymes with at least one meal each week. One-fifth of patients missed taking enzymes during at least 3 meals per week. (Mean age = 9.8 ± 4.1, mean % weight for height = 97 ± 9.5)

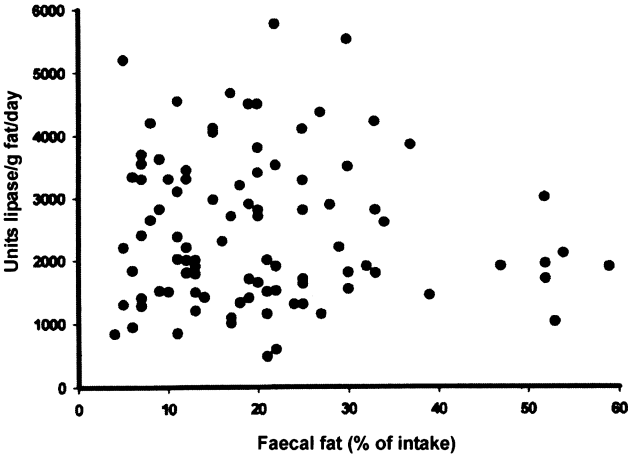


Figure 7 **Enzyme intake (units lipase/g fat/day) plotted against faecal fat (% of intake) among 43 patients with pancreatic insufficiency (mean age 21.2 years, range 7–41.9 years).** A total of 94 observations were made. All patients were receiving enteric coated enzyme products in doses the individual patient and/or caregiver perceived to be appropriate. Mean enzyme intake was highly variable (range 477–5765 lipase units/g fat/day). There was no correlation between lipase intake and faecal fat (% of intake). Fat losses ranged from 4 to 59% of fat intake. Similar results were obtained when enzyme intake was plotted against faecal energy losses (% of intake) determined by bomb calorimetry (data not shown). $r = -0.06$, $P > 0.5$

particularly teenagers, do not take their enzymes on a regular basis. Asking a child a simple question—how often do you miss taking your enzymes?—particularly when the parents are not present, may provide revealing insights!

Patients with CF commonly suffer from abdominal symptoms such as bloating, abdominal pain and bulky malodorous stools. Abdominal symptoms may be due to a CF related cause, or due to a number of unrelated gastrointestinal abnormalities. Caregivers should not assume that abdominal symptoms are due to ineffective or inadequate enzyme therapy. Consequently, arbitrary increases in the enzyme dose should not be considered without careful evaluation for alternative causes of symptoms and objective evidence evaluating efficacy of response. Whenever there is doubt concerning efficacy of therapy, a 72-h fat balance study, while carefully recording enzyme and nutrient intake is indicated. As shown in Figure 7 the results are likely to be quite revealing. These data are a compilation of three prospective double-blind studies which assessed efficacy of various enzyme preparations among CF patients who had symptoms of maldigestion and/or poor weight gain[64]. A total of 94 observations were made among 43 patients with pancreatic insufficiency (mean age 21.2 years, range 7–41 years). Seventy-two hour stool collections were analysed for wet weight, fat and energy absorption. Dietary intake was weighed and enzyme dose recorded. All the patients were receiving enteric coated enzyme products in doses the individual patient and/or their caregiver perceived to be appropriate. Mean enzyme intake was 2475 ± 1191 lipase units/gram fat/day (range 477–5765 lipase units per gram fat per day). On average, fat malabsorption was 20%, but fat losses ranged from 4–59%. Only 18 of 94 measurements were < 10% of intake and 14 of 94 showed losses greater than 30% of intake. What was even more surprising was the lack of any correlation between enzyme dose and faecal losses of fat. Similar results were obtained when enzyme intake was plotted against faecal energy losses determined by bomb calorimetry (data not shown). Symptoms commonly associated with maldigestion such as frequent bulky bowel movements, abdominal pain or bloating were not predictive of efficacy. It remains possible that some of these patients would have benefited from higher doses of enzymes; others may have benefited from adjunctive therapy with gastric acid inhibitors or combining conventional enzymes with enteric coated products. The overall results of this analysis point to the inaccuracy of qualitative assessment of enzyme needs based on symptoms and argue strongly for objective reassessment following any change in treatment.

In our view, individual patients should be reviewed, at least annually to reinforce the need for compliance, and to determine whether patterns of ingestion are acceptable. As children grow older, they should be encouraged to assume greater responsibility for their own enzyme therapy. This, in turn, means that caregivers need to develop useful 'strategies' to re-educate the affected patient and reinforce the need for effective therapy.

Acknowledgment Much of the work described in this manuscript was supported by the Canadian Cystic Fibrosis Foundation.

REFERENCES

1 Gaskin K, Gurwitz D, Durie P, Corey M, Levison H, Forstner G. Relationship of nutrition and pulmonary function in cystic fibrosis [Letter]. *J Pediatr* 1983;**103**:164–5

2 Kopelman HR, Corey M, Gaskin KJ, Durie P, Forstner GG. Impaired chloride secretion, as well as bicarbonate secretion, underlies the fluid secretory defect in the cystic fibrosis pancreas. *Gastroenterology* 1988;**95**:349–55

3 Gaskin KJ, Durie P, Lee L, Hill R, Forstner GG. Co-lipase and lipase secretion in childhood onset of pancreatic insufficiency: delineation of patients with steatorrhea secondary to relative co-lipase deficiency. *Gastroenterology* 1984;**86**:1–7

4 Waters DR, Dorney SFA, Gaskin KJ, Gruca MA, O'Halloran M, Wilcken B. Pancreatic function in infants identified as having cystic fibrosis in a neonatal screening program. *N Engl J Med* 1990;**322**:303–8

5 Couper R. Pancreatic Function Tests. In: Walker WA, Durie PR, Hamilton JR, Walker-Smith JA, Watkins JB, eds. *Pediatric Gastrointestinal Disease. Pathophysiology, Diagnosis, Management*, 2nd edn. St Louis, MO: Mosby-Year Book Inc., 1996: 1621–34

6 DiMagno EP, Go VLW, Summerskill WHJ. Relations between pancreatic enzyme outputs and malabsorption in severe pancreatic insufficiency. *N Engl J Med* 1973;**288**:813–15

7 Lundh G. Pancreatic function in neoplastic and inflammatory disease: a simple reliable new test. *Gastroenterology* 1962;**42**:275–80

8 Khouri MR, Huang G, Shiau YF. Sudan stain of fecal fat: new insight into an old test. *Gastroenterology* 1989;**96**:421–7

9 Colombo C, Maiavacca R, Ronchi M, Consalvo E, Amoretti M, Giunta A. The steatocrit: a simple method for monitoring fat malabsorption in patients with cystic fibrosis. *J Pediatr Gastroenterol Nutr* 1987;**6**:926–30

10 American Society for Test Materials. *Standards for Bomb Calorimetry*. Milona, Illinois: Parr Instrument Co, 1974

11 van der Kamer JK, Huininch H, Weyers HA. Rapid method for determining fat in feces. *J Biol Chem* 1949;**177**:347–55

12 Murphy JL, Wootton SA, Bond SA, Jackson AA. Energy content of stools in normal healthy controls and patients with cystic fibrosis. *Arch Dis Child* 1991;**66**:495–500

13 Dyck WP. Titremetric measurements of fecal trypsin and chymotrypsin in cystic fibrosis with pancreatic insufficiency. *Am J Dig Dis* 1967;**12**:310–17

14 Remtulla M, Durie PR, Goldberg DM. Is chymotrypsin output a better diagnostic index than measurement of chymotrypsin in random stool? *Enzyme* 1988;**39**:190–8

15 Stein J, Jung M, Sziegolt A, *et al.* Immunoreactive elastase 1: clinical evaluation of a non-invasive test of pancreatic function. *Clin Chem* 1996;**42**:222–6

16 Soldan W, Henker J, Sprössig C. Sensitivity and specificity of quantitative determination of pancreatic elastase 1 in feces of children. *J Pediatr Gastroenterol Nutr* 1997;**24**:53–5

17 Perman JA, Montes RG. Breath tests. In: Walker WA, Durie PR, Hamilton JR, Walker-Smith JA, Watkins JB, eds. *Pediatric Gastrointestinal Disease. Pathophysiology, Diagnosis, Management*, 2nd edn. St Louis, MO: Mosby-Year Book, 1996: 1635–45

18 Hiele M, Rutgeerts P, Vantrappen G. Starch digestion in normal subjects and patients with pancreatic disease using a $13CO_2$ breath test. *Gastroenterology* 1989;**60**:503–9

19 Watkins JB, Klein PD, Schoeller DA, Kirschner BS, Park R, Perman JA. Diagnosis and differentiation of fat malabsorption in children using ^{13}C-labelled lipids: Trioctanoin, Triolein and Palmitic acid breath tests. *Gastroenterology* 1982;**82**:811–907

20 Amarri S, Harding M, Coward WA, Evans TJ, Weaver LT. ^{13}Carbon mixed triglyceride breath test and pancreatic enzyme supplementation in cystic fibrosis. *Arch Dis Child* 1997;**76**:349–51

21 Imondi AR, Stradley RP, Wolgemuth R. Synthetic peptides in the diagnosis of exocrine pancreatic insufficiency in animals. *Gut* 1972;**13**:728–31

22 Toskes PP. Bentiromide as a test of pancreatic function in adult patients with pancreatic exocrine insufficiency: determination of appropriate dose and urinary collection interval. *Gastroenterology* 1983;**85**:565–9

23 Weizman Z, Forstner GG, Gaskin KJ, Kopelman H, Wong S, Durie P. The Bentiromide test for assessing pancreatic dysfunction using analysis of PABA in plasma and urine: studies in cystic fibrosis and Shwachman's syndrome. *Gastroenterology* 1985;**89**:596–604

24 Laufer D, Cleghorn G, Ellis L, Koren G, Forstner GG, Durie PR. The Bentiromide test using plasma PABA for diagnosing pancreatic insufficiency in young children. *Gastroenterology* 1991;**101**:207–13

25 Cleghorn GJ, Benjamin L, Forstner GG, Dati F, Durie P. Serum immunoreactive pancreatic lipase and cationic trypsinogen in the assessment of pancreatic function in older patients with cystic fibrosis. *Pediatrics* 1986;**77**:301–6

26 Durie P, Forstner GG, Gaskin KJ, Moore DJ, Cleghorn GJ, Wong SS, *et al.* Age-related alterations of immunoreactive pancreatic cationic trypsinogen in sera from CF patients with and without pancreatic insufficiency. *Pediatr Res* 1986;**20**:209–13

27 Couper RTL, Corey M, Durie PR, Forstner GG, Moore DJ. Longitudinal evaluation of serum trypsinogen measurement in pancreatic-insufficient and pancreatic sufficient patients with cystic fibrosis. *J Pediatr* 1995;**127**:408–13

28 Kerem E, Corey M, Kerem BS, Rommens J, Markiewicz D, Levison H, *et al.* The relation between genotype and phenotype in cystic fibrosis: analysis of the most common mutation (ΔF508). *N Engl J Med* 1990;**323**:1517–22

29 Kristidis P, Bozon D, Corey M, Markiewicz D, Rommens J, Tsui L-C, Durie P. Genetic determination of exocrine pancreatic function in cystic fibrosis. *Am J Hum Genet* 1992;**50**:1178–84

30 Borowitz DS, Grand RJ, Durie PR and the Consensus Committee. Use of pancreatic enzyme supplements for patients with cystic fibrosis in the context of fibrosing colonopathy. *J Pediatr* 1995;**127**:681–4

31 Twarog FJ, Weinstein SF, Khaw K-T, Strieder DJ, Colten HR. Hypersensitivity to pancreatic extracts in parents of patients with cystic fibrosis. *J Allergy Clin Immunol* 1997;**59**:35–40

32 Stapleton FB, Kennedy J, Nousia-Arvanitakis S, Linshaw MA. Hyperuricosuria due to high dose pancreatic extracts in cystic fibrosis. *N Engl J Med* 1976;**295**:246–8

33 Davidson GP, Morad-Hassel F, Crozier D, Corey M, Forstner G. Iatrogenic hyperuricemia in children with cystic fibrosis. *J Pediatr* 1978;**93**:976–8

34 Smyth RL, van Velzen D, Smyth AR, Lloyd DA, Heaf DP. Strictures of the ascending colon in cystic fibrosis and high strength enzymes. *Lancet* 1994;**343**:85–6

35 Smyth RL, Ashby D, O'Hea U, *et al.* Fibrosing colonopathy in cystic fibrosis: results of a case control study. *Lancet* 1995;**346**:1247–51

36 FitzSimmons SC, Burkhart GA, Borowitz D, *et al.* High-dose pancreatic enzyme supplements and fibrosing colonopathy in children with cystic fibrosis. *N Engl J Med* 1997;**336**:1283–89

37 Layer P, Go VLW, DiMagno EP. Fate of pancreatic enzymes during small intestinal aboral transit in humans. *Am J Physiol* 1986;**251**:G475–G480

38 Thiruvengadam R, DiMagno EP. Inactivation of human lipase by proteases. *Am J Physiol* 1988;**255**:G476–G481

39 Kraisinger M, Hochhaus G, Stecenko A, Bowser E, Hendeles L. Clinical pharmacology of pancreatic enzymes in patients with cystic fibrosis and *in vitro* performance of microencapsulated formulations. *J Clin Pharmacol* 1994;**34**:158–66

40 O'Hare MMT, McMaster C, Dodge JA. Stated versus actual lipase activity in pancreatic enzyme supplements: implications for clinical use. *J Pediatr Gastroenterol Nutr* 1995;**21**:59–63

41 Graham DY. Enzyme replacement therapy of exocrine pancreatic insufficiency in man. *N Engl J Med* 1977;**296**:1314–17

42 DiMagno EP, Malagelada JR, Go VLW, Moertel CG. Fate of orally ingested enzymes in pancreatic insufficiency: comparison of two dosage schedules. *N Engl J Med* 1977;**296**:1318–22

43 Zerega J, Lerner S, Meyer JH. Duodenal instillation of pancreatin does not abolish steatorrhea in patients with pancreatic insufficiency. *Digest Dis Sci* 1988;**33**:1245–9

44 Youngberg CA, Berardi RR, Howatt WF, *et al.* Comparison of gastrointestinal pH in cystic fibrosis and healthy subjects. *Digest Dis Sci* 1987;**32**:472–80

45 Robinson PJ, Smith AL, Sly PD. Duodenal pH in cystic fibrosis and its relationship to fat malabsorption. *Digest Dis Sci* 1990;**35**:1299–304

46 Graham DY. Pancreatic enzyme replacement: the effect of antacids or cimetidine. *Digest Dis Sci* 1982;**27**:485–90

47 Durie PR, Bell L, Linton W, Corey ML, Forstner GG. Effect of cimetidine and sodium bicarbonate on pancreatic replacement therapy in cystic fibrosis. *Gut* 1980;**21**:778–86

48 Boyle BJ, Long WB, Balistreri WF, Widzer SJ, Huang N. Effect of cimetidine and pancreatic enzymes on serum and fecal bile acids and fat absorption in cystic fibrosis. *Gastroenterology* 1980;**78**:950–3

49 Cox KL, Isenberg JN, Osher AB, Dooley RR. The effect of cimetidine on maldigestion in cystic fibrosis. *J Pediatr* 1979;**94**:488–92

50 Schöni M, Kraemer R, Ruedeberg A, *et al.* Long-term cimetidine in children with cystic fibrosis: a randomized double-blind study. *Pediatr Res* 1984;**18**:66–70

51 DiMagno EP. Controversies in the treatment of exocrine pancreatic insufficiency. *Digest Dis Sci* 1982;**27**:481–4

52 Gow R, Bradbear R, Francis P, Shepherd RW. Comparative study of varying regimens to improve steatorrhoea and creatorrhoea in cystic fibrosis: effectiveness of an enteric-coated preparation with and without antacids and cimetidine. *Lancet* 1981;**ii**;1071–4

53 Stead RJ, Skypala I, Hodson ME, Batten JC. Enteric-coated microspheres of pancreatin in the treatment of cystic fibrosis: comparison with a standard enteric-coated preparation. *Thorax* 1987;**42**:533–7

54 Dutta SK, Hubbard VS, Appler M. Critical examination of therapeutic efficacy of a pH-sensitive enteric-coated pancreatic enzyme preparation in treatment of exocrine pancreatic insufficiency secondary to cystic fibrosis. *Digest Dis Sci* 1988;**33**:1237–44

55 Beverley DW, Kelleher J, MacDonald A, Littlewood JM, Robinson T, Walters MP. Comparison of four pancreatic extracts in cystic fibrosis. *Arch Dis Child* 1987;**62**:564–8

56 Robinson PJ, Olinsky A, Smith AL, Chitravanshi SB. High compared with standard dose lipase pancreatic supplement. *Arch Dis Child* 1989;**64**:143–5

57 Brady MS, Rickard K, Yu P-L, Eigen H. Effectiveness and safety of small vs. large doses of enteric coated pancreatic enzymes in reducing steatorrhea in children with cystic fibrosis: a prospective randomized study. *Pediatr Pulmonol* 1991;**10**:79–85

58 Gan KH, Heijerman HGM, Geus WP, Bakker W, Lamers CBHW. Comparison of a high lipase pancreatic enzyme extract with a regular pancreatin preparation in adult cystic fibrosis patients. *Aliment Pharmacol Ther* 1994;**8**:603–7

59 Lancellotti L, Cabrini G, Zanolla L, Mastella G. High- versus low-lipase acid resistant enzyme preparation in cystic fibrosis: a crossover randomized clinical trial. *J Pediatr Gastroenterol Nutr* 1996;**22**:73–8

60 Meyer JH, Elashoff V, Porter-Fink J, Dressman, Amidon GL. Human postprandial gastric emptying of 1–3-millimeter spheres. *Gastroenterology* 1988;**94**:1315–25

61 Ellis L, Durie P, Corey M, Davis L, Kalnins D. Changing the coating of pancreatic enzyme microspheres to dissolve at a lower pH does not improve efficacy [Abstract]. *Pediatr Pulmonol* 1994; Suppl 10:273

62 Zentler-Munro PL, Fine DR, Fitzpatrick WJF, Northfield TC. Effect of intrajejunal acidity on lipid digestion and aqueous solubilisation of bile acids and lipids in health, using a new simple method of lipase inactivation. *Gut* 1984;**25**:491–9

63 Zentler-Munro PL, Fine DR, Batten JC, Northfield TC. Effect of cimetidine on enzyme inactivation, bile acid precipitation, and lipid solubilisation in pancreatic steatorrhoea due to cystic fibrosis. *Gut* 1985;**26**:892–901

64 Ellis L, Kalnins D, Corey M, Pencharz P, Durie P. Correlation between fecal weight, fecal fat and fecal energy in patient with cystic fibrosis [Abstract]. *Pediatr Pulmonol* 1997; Suppl 14:307