IMPACT OF GASTROSTOMY TUBE FEEDINGS ON SURVIVAL IS AFFECTED BY PULMONARY FUNCTION IN INDIVIDUALS WITH CYSTIC FIBROSIS

By

ELIZABETH S. BEASLEY

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Elizabeth S. Beasley

This thesis is dedicated to the children with cystic fibrosis in hopes that there may one day be a cure for this devastating disease.

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TABLE OF CONTENTS

page

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

ABC transporter – adenosine triphosphate-binding cassette transporter

ATP – adenosine triphosphate

BMD – bone mineral density

BMI – body mass index

cAMP – cyclic adenosine monophosphate

CF – cystic fibrosis

CFLD – cystic fibrosis-associated liver disease

CFRD – cystic fibrosis related diabetes mellitus

CFTR – cystic fibrosis transmembrane conductance regulator

DIOS – distal intestinal obstruction syndrome

DNA – deoxyribonucleic acid

EFA – essential fatty acid

$FEF_{25-75\%}$ –- forced expiratory flow at 25-75% forced vital capacity

FEV_1 – forced expiratory volume in one second

FFM – fat free mass

FVC – forced vital capacity

g/d – grams per day

GT – gastrostomy tube

GTA – gene transfer vector

IBW – ideal body weight

IU – international units

kg – kilogram

LA – linoleic acid

NTx – N-telopeptides of type I collagen

PC – phosphatidlycholine

PEG – percutaneous endoscopic gastrostomy

PI – pancreatic insufficient

PS – pancreatic sufficient

PSU – psuedouridine

R-domain – regulatory domain

REE – resting energy expenditure

TG – triacylglycerol

TNF-α – tumor necrosis factor alpha

Abstract of Thesis Presented to the Graduate School
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By

Elizabeth S. Beasley

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Chair: Gail Kauwell
Major Department: Food Science and Human Nutrition

Cystic fibrosis (CF) is an autosomal recessive disease caused by an abnormal gene on chromosome 7 that codes for the cystic fibrosis transmembrane conductance regulator (CFTR). This genetic mutation prevents proper transport of chloride ions through membrane channels resulting in the secretion of thick mucus from the exocrine glands, which compromises gastrointestinal and pulmonary function and nutritional status. Maintenance or improvement of nutritional status is viewed as important for overall health and in preserving lung function in individuals with CF. Gastrostomy tube (GT) feeding is one option available to aid in maintaining or improving nutritional status when nutrient and energy needs are not met by oral feeding. Practice standards defining the timing of initiation of GT feeding in patients with CF have not been developed and may account for conflicting results from studies evaluating the effectiveness of GT feedings.

A retrospective chart review of CF subjects who received care from the UF Pediatric Pulmonary Center between 1990-2002 was conducted to examine the hypothesis that the timing of GT feeding initiation influences survival outcomes for individuals with CF. Changes in weight, pulmonary function, and number of hospitalizations 12 months pre- and post-GT feeding were evaluated in 21 subjects (9 males and 12 females) who met the inclusion criteria.

Small airway function, as measured by $FEF_{25-75\%}$, was significantly improved by GT feeding, but no significant change in the number of days hospitalized or body weight was detected. However, there was a trend for improvement in weight, as well as other measurements of pulmonary function. Moreover, no significant differences were detected between survivors and non-survivors for body mass index (BMI). Hazard ratios based on BMI, pulmonary function, and gender suggested greater mortality for females versus males. At the time of GT feeding initiation, survivors had significantly lower ($p < 0.05$) pulmonary function compared to non-survivors, and individuals with an FEV_1 <40% predicted had a two-fold higher mortality risk than subjects with an FEV_1 >40% predicted. Body mass index at the time of GT feeding initiation did not appear to affect survival. Although GT feeding does not appear to improve pulmonary function or weight, initiation of GT feeding before FEV_1 is below 40% may improve patient survival. A multi-center study confirming these results could serve as the basis for developing practice standards that could benefit patients with CF.

CHAPTER 1
INTRODUCTION

Cystic fibrosis (CF) is a multisystem disorder that primarily afflicts Caucasians with an incidence of 1:2500 live births (Cystic Fibrosis Foundation 2002). It is caused by an abnormal gene on chromosome 7 that codes for the cystic fibrosis transmembrane conductance regulator (CFTR). This genetic mutation prevents the proper transport of chloride ions through membrane channels resulting in the secretion of thick mucus from exocrine glands (Lees & Smyth 2000, National Cystic Fibrosis Research Foundation 1971, Rossi & Stoll 1968). The abnormal mucus production and secretion associated with CF impair the function of multiple organ systems, particularly the respiratory and gastrointestinal tracts. Pancreatic insufficiency, secondary to mucus plugs that obstruct the pancreatic ducts, occurs in 85% of individuals with CF. Maldigestion and malabsorption, both of which can negatively impact nutrition status and growth, are associated with pancreatic insufficiency (Lees & Smyth 2000). Mucus production also has an adverse effect on pulmonary function because it is associated with repeated respiratory tract infections, airway inflammation, and respiratory failure. Pulmonary function, as measured by forced expiratory volume in one second (FEV_1), is the main determinant of morbidity and mortality in patients with CF (Rosenfeld et al. 2001).

Several research groups have noted a relationship between lack of adequate nutrient intake and decreased pulmonary function. Ramsey and

colleagues (1992) observed that anorexia, elevated metabolic rate, and subsequently, elevated energy requirements are associated with chronic pulmonary infections. Individuals with CF and chronic pulmonary disease have an increase in protein catabolism, which further increases the need for adequate nutrient intake (Dodge 1988). Pulmonary exacerbations also may contribute to anorexia and reduced nutrient intake in individuals with CF secondary to nausea and vomiting and a general feeling of poor health. Individuals with severe lung disease may exhibit an aversion to food secondary to physical fatigue, clinical depression, and/or altered sense of smell (Stallings et al. 1994). In addition to a decline in pulmonary muscle function, malnutrition in individuals with CF also is associated with impaired immune function (Dalzell et al. 1991, Shepherd et al. 1980). Compromised nutritional status may negatively impact survival as suggested by Kerem and colleagues (1992) who observed that CF patients whose weight-for-height percentile fell below the 70th percentile had a two-year mortality rate that was 50% higher than patients with a weight-for-height percentile above the 70th percentile.

Nutrition supplementation with gastrostomy tube (GT) feedings is one option available to aid in maintaining or improving nutritional status when nutrient and energy needs are not met by oral feeding. Practice standards defining the timing of initiation of GT feeding in patients with CF have not been developed and may account for conflicting results from retrospective studies evaluating the effectiveness of GT feedings. In many of these studies, GT feeding was initiated in malnourished individuals with severe pulmonary disease. Initiation of GT

feeding late in the disease process may not be reflective of the outcomes that potentially occur with earlier intervention. For example, although increases in body weight were reported in some studies, failure to achieve clinically optimal weight gain may be due to delayed initiation of feeding. In contrast, stabilization of pulmonary function noted in patients with severe lung disease but not in patients with mild/moderate lung disease may be related to the natural course of the disease rather than the influence of GT feeding (Gaskin 1988, Steinkamp & von der Hardt 1994, Vaisman et al. 1991, Williams et al. 1999).

Adequate nutrition and maintenance of pulmonary status are essential to health maintenance in patients with CF. Instead of using GT feeding as a last resort, it is possible that early intervention with GT feeding may improve survival of patients with CF (Walker & Gozal 1998). Identifying which measures of nutritional status and/or pulmonary function and the level of function at the time of GT placement that are associated with survival would be helpful to the CF team in making an evidence-based decision about the timing of GT feeding initiation.

Hypothesis

Timing of GT feeding initiation influences survival outcome for individuals with CF.

Specific Aim

The specific aims of the study are to evaluate the effects of GT feeding on height, weight, pulmonary status, and number of days hospitalized per month by comparing rates of change 12 months prior to GT placement through 12 months following GT placement; and to identify which measures of nutritional status

and/or pulmonary function and the level of status/function at the time of GT placement are associated with survival.

CHAPTER 2
BACKGROUND AND LITERATURE REVIEW

Cystic Fibrosis

Cystic fibrosis (CF) is a multisystem disease with an incidence of 1:2500 live Caucasian births. It affects 22,732 people in the United States, 95.3% of whom are Caucasian (Cystic Fibrosis Foundation 2002). Approximately 5% of Caucasian Americans are carriers for CF (Welsh & Smith 1995). The current predicted median survival age is 33.4 years in the United States and 40 years in the United Kingdom, a dramatic improvement compared to data from 1969 when the median survival age was 14 years (Cystic Fibrosis Foundation 2002, Lees & Smyth 2000). This improvement in survival is attributed to earlier diagnosis, pancreatic enzyme replacement therapy, aggressive pulmonary therapy, and greater attention focused on improving nutritional status (Elborn et al. 1991, Lees & Smyth 2000, Levine 1998).

Cystic Fibrosis Genotype

CF is an autosomal recessive disease caused by an abnormal gene in the region of q31-32 on the long arm of chromosome 7. This gene codes for the cystic fibrosis transmembrane conductance regulator (CFTR) (Zielenski 1991). CFTR is a protein generally referred to as an ATP-binding cassette transporter (ABC transporter). CFTR is located on the external membrane of various cells in the lungs, pancreas, colon, epithelial tissue, and genitourinary tract. The CFTR forms a channel for chloride passage, which is necessary for sodium chloride

production (Sheppard & Welsh 1999, Welsh & Smith 1995). This protein is unique from other ABC transporters because it contains five domains instead of the usual four. Two domains are membrane-spanning and create the chloride channel, two domains are nucleotide-binding and are responsible for hydrolyzing ATP, and the final domain is a regulatory domain (R domain), which is not commonly present in this type of transporter (Sheppard & Welsh 1999). In order for chloride to move through this channel, the two nucleotide-binding domains must attach to ATP followed by cleavage of the phosphate groups by cAMP-dependent protein kinase. The phosphate groups from the cleaved ATP phosphorylate serine residues on the regulatory domain, which opens the membrane channel allowing chloride transport. Channel regulation is controlled by ATP hydrolysis at the nucleotide-binding domains. Once the R domain is dephosphorylated by protein phosphatases the channel returns to its prior dormant state (Sheppard & Welsh 1999, Welsh & Smith 1995).

There are over 1,000 mutations that result in CF. The CFTR mutations are classified into six subsets: (1) no synthesis of CFTR, (2) incorrect processing, (3) defective regulation, (4) conductance abnormalities, (5) defective regulation of other channels, and (6) partially defective production or processing. Classifications 1-3 are associated with pancreatic insufficiency and are the most common. Overall, the most common and severe mutation is the ΔF508 mutation, which affects ~70% of the CF Caucasian population (NIH Consensus Statement 1997, Ratjen & Doring 2003). This mutation occurs in the portion of the DNA molecule that codes for the first nucleotide-binding domain. The ΔF508 mutation

is characterized by the absence of three base pairs from the CFTR gene. The absence of these nucleotides causes the protein product of the gene to lack phenylalanine at amino acid position 508 (Hatta et al. 2002, Sheppard & Welsh 1999). This mutation is associated with the most severe form of CF because the altered protein is largely trapped in the endoplasmic reticulum. Other mutations of the CFTR gene result in less severe forms of the disease because the CFTR protein is able to leave the endoplasmic reticulum and travel to the cell membrane (NIH Consensus Statement 1997, Rombeau & Rolandelli 1997, Welsh & Smith 1995).

The defect in the CFTR gene product arising from the ΔF508 mutation results in the production of a thick, viscous mucus from the exocrine glands, causing obstruction of glands and ducts of multiple organs including the pancreas, lungs, and reproductive organs. These secretions can result in bronchiectasis, exocrine pancreatic enzyme deficiency, high sweat electrolytes, and decreased fertility (Lees & Smyth 2000, National Cystic Fibrosis Research Foundation 1971, Rossi & Stoll 1968).

Diagnosis of Cystic Fibrosis

The median age at the time of CF diagnosis in 2001 was 6 months (Cystic Fibrosis Foundation 2002). Early symptoms of CF include meconium ileus, failure to thrive, celiac disease, rectal prolapse, malabsorption, chronic pneumonia, chronic cough, and excessive sodium and chloride in sweat. In the pediatric cohort, CF is diagnosed based on signs, symptoms, and a sweat test, the later of which is a quantitative analysis of the chloride and sodium

concentration of sweat. This test is conducted by placing electrodes on the forearm, covering the area with a gauze bandage saturated with a drug called pilocarpine, and wrapping the area in plastic. Application of an electric current to the skin causes the drug to stimulate the sweat glands to produce sweat. A piece of filter paper is placed on the forearm to absorb the sweat. The filter paper is analyzed to determine the concentrations of sodium and chloride. Sodium and chloride concentrations exceeding 70 mEq/L and 60 mEq/L, respectively, are considered diagnostic for CF. This test is more than 99% predictive for CF in children. The sweat test is not commonly used in adults. Instead, CF is typically diagnosed in adults using genetic testing to determine if mutations in the CF gene are present (Hopkin 1998, National Cystic Fibrosis Research Foundation 1971, Shale 1996).

Pathophysiology of Cystic Fibrosis

Mucus secretions primarily affect the respiratory tract, gastrointestinal tract, sweat and salivary glands, and the reproductive tract; however, other organ systems also are affected adversely by CF. Especially important in determining patient treatment are the effects of CF on the gastrointestinal and respiratory tracts (Ratjen & Doring 2003).

Hepatobiliary Function

Meconium ileus, observed in 15% of newborns with CF, and jaundice with cholestasis is observed secondary to lodged secretions in the bile ducts. As CF progresses, mucus accumulation can result in intra- and extrahepatic biliary stones, which may cause obstruction. Mucus-containing cysts can be found in the gallbladder due to mucoid material accumulation in the lumen. In addition,

microgallbladder and cholecystitis are common secondary conditions found in individuals with CF. These conditions are becoming more widespread as the lifespan of individuals with CF increases. Liver pathophysiology, represented as bile-duct stenosis with sclerosing cholangitis, also is common in CF and may lead to the development of cirrhosis. Portal hypertension, esophageal varices, and hypersplenism may present secondary to liver pathophysiology. However, death resulting from liver cirrhosis is rare, occurring in only 1-2% of individuals with CF (Hodson & Geddes 2000, Orenstein 1997).

Cardiovascular Function

Most cardiovascular malfunctions occur following pulmonary hypertension and respiratory failure. Cor pulmonale can occur as CF progresses and may cause portions of the myocardium to become fibrotic. Interestingly, CF individuals have a lower incidence of aortic artherosclerosis than non-CF age-matched controls. This phenomenon is attributed to chronic infection and fat malabsorption (Hodson & Geddes 2000).

Reproductive Function

Females and males with CF undergo puberty and develop secondary sexual characteristics; however, puberty may be delayed 1 to 2 years secondary to poor nutritional and pulmonary status. Females with CF have less fluid in their cervical mucus, which may make it more difficult to become pregnant. However, most women with CF are able to conceive and have normal deliveries of healthy babies. Pathology commonly observed in women with CF includes multiple follicular cysts, cervicitis, mucous gland hyperplasia, and cervical erosions (Hodson & Geddes 2000, Orenstein 1997).

Males with CF typically are infertile secondary to obstructed or atretic vas deferens. Furthermore, there is abnormal dilation or absence of the body and tail of the epididymes and seminal vesicles. These structural anomalies have no explanation, but it has been suggested that the CFTR may affect spermatogenesis, as well as development of the vas deferens (Hodson & Geddes 2000, Orenstein 1997).

Pancreatic Function

Exocrine pancreatic insufficiency afflicts 85% of the CF population (Kulczycki et al. 2002). This insufficiency develops as a result of the production of thick, viscous mucus, which obstructs the pancreatic ducts. Pancreatic duct obstruction prevents pancreatic enzymes from reaching the small intestine, resulting in maldigestion and malabsorption of dietary protein, fat, and other vitamins and minerals. Eventually, fibrous tissue and cysts replace the pancreatic lobules. Not all CF mutations cause pancreatic insufficiency (PI). For example, the G551S and P574H mutations are pancreatic-sufficient (PS) dominant mutations; however, CF patients with PS mutations should have annual evaluations to confirm that they have not become pancreatic insufficient as their disease progresses (Borowitz et al. 2002). Recurrent pancreatitis, secondary to CF, is common in both pancreatic insufficient and pancreatic sufficient individuals. This condition is attributed to autodigestion of the pancreas by pancreatic enzymes retained as a result of obstruction of the pancreatic ducts (Hodson & Geddes 2000).

Endocrine function of the pancreas also can be affected by CF. CF related diabetes mellitus (CFRD) occurs in 15% of all CF patients and can develop as

CF progresses. This condition is considered the primary comorbid factor in individuals with CF (FitzSimmons 1993, Lees & Smyth 2000). CFRD is caused by mucus obstruction of pancreatic beta cells, which prevents insulin secretion and may lead to beta cell destruction. Insulin therapy can be used to control CFRD (Hopkin 1998). Inadequately controlled CFRD and subsequent glucosuria contribute to energy loss (Stallings et al.1994). According to the Cystic Fibrosis Foundation Patient Registry Annual Data Report 2001, approximately 25% of CF individuals over the age of 35 years have CF-related diabetes (2002).

Gastrointestinal Function

Gastroesophageal reflux and esophagitis are commonly seen in individuals with CF. Lesions in the labial and salivary glands also are frequently observed in combination with eosinophilic plugs in the ducts. Distal intestinal obstruction syndrome (DIOS), characterized by blockage in the ileum or colon, can be problematic in individuals with compromised hydration status who are using pancreatic enzyme replacement therapy (Hodson & Geddes 2000). A rare complication of DIOS called intussusception can occur when a portion of the intestine telescopes into another section of the intestine. This phenomenon is likely due to adherence of sticky mucus and stool inside the intestine and peristalsis causing the intestine to move along with the digested food (Orenstein 1997). Individuals with CF also are at risk for rectal prolapse since malnutrition negatively affects the support structures of the rectum and chronic coughing or straining during bowel movements can force the rectum outside of the anus (Orenstein 1997). Typically rectal prolapse resolves after 5 years of age. Aside from the aforementioned gastrointestinal concerns, individuals with CF also are

at increased risk for developing gastrointestinal adenocarcinoma; however, the risk for developing other forms of cancer is equivalent to non-CF individuals (Hodson & Geddes 2000, Neglia et al. 1991).

Pulmonary Function

Pulmonary function is the main indicator of patient morbidity and mortality. Over 95% of CF deaths are related to respiratory failure (Lees & Smyth 2000). Mucus in the respiratory tract causes repeated infections, often by bacterial colonization of *Pseudomonas aeruginosa*. Chronic infection with *Burkholderia cepacia,* a multiresistant microbe, also is associated with increased morbidity and mortality in individuals with CF (Cystic Fibrosis Foundation 1994). Mucus in the respiratory tract causes airway inflammation, secondary to extensive neutrophil penetration, and bronchiectasis (Kennedy 2001, Rosenfeld et al. 2001). Studies have shown that airway inflammation in individuals with CF begins as early as four weeks of age. This inflammation is caused by an abundance of neutrophils in the lungs. More specifically, neutrophils release neutrophil elastase, which degrades structural proteins, such as elastin, and can cause the development of bronchiectasis. Furthermore, there are high levels of proinflammatory chemokines and cytokines, but a depressed amount of the anti-inflammatory cytokine normally produced by bronchial epithelial cells called interleukin-10 (Kennedy 2001). A secondary effect of lung infections is digital clubbing, characterized by swelling of the tips of the toes and fingers. The precise pathophysiology of digital clubbing is not presently known; however, it is generally observed that as lung function decreases the digital clubbing worsens (Hopkin 1998, Orenstein 1997). One hypothesis generated to explain the

development of digital clubbing is that substances from lung infections enter the bloodstream and stimulate soft tissue positioned at the bottom of the nail.

Pulmonary status is evaluated using a type of predictive testing called spirometry. Spirometry includes measurement of forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), and forced expiratory flow at 25 to 75% of vital capacity ($FEF_{25 \text{ to } 75\%}$) (Orenstein 1997). FEV_1 is the measurement typically used to evaluate the severity of lung disease. Normal lung function is >90% predicted FEV_1, mild is 70-89%, moderate is 40-69, and <40 is severe (Cystic Fibrosis Foundation 2002). The standard value for FVC, the amount of air exhaled after a maximum inhalation, is >85% predicted. The normal value for $FEF_{25 \text{ to } 75\%}$ is >65% predicted (Orenstein 1997, Rosenfeld et al. 2001, Stapleton et al. 2001). Expressing pulmonary status as a percentage of the predicted value for age, gender, height, and race from regression equations based on a reference group is often used for analysis because it allows comparison among individuals and longitudinal comparison of changes within an individual (Rosenfeld et al. 2001, Stapleton et al. 2001). One study with 673 CF subjects monitored from 1977 to 1989 reported that FEV_1 below 30% of the predicted value or FVC below 40% predicted value was indicative of a two-year mortality rate greater than 50% (Kerem et al. 1992).

Nutrition Related Complications of Cystic Fibrosis

Malnutrition and Growth

In general, CF induced malnutrition can be attributed to three main causes, increased energy loss, increased energy expenditure, and decreased energy intake (Stallings et al. 1994). Malnutrition is associated with a reduction in growth

rate as reflected by the weight for height ratio in infants and children (Bishop et al. 1999, National Cystic Fibrosis Research Foundation 1971). For patients with CF, assessment of nutritional status is based in part on percent IBW, with acceptable nutritional status, at-risk, and nutritional failure defined as $\geq$90%, $\geq$90% with weight loss or weight plateau, and <90%, respectively (Borowitz 2002).

Studies show that CF induced malnutrition can adversely affect linear growth during childhood. Karlberg et al. (1992) assessed linear growth in 51 children with CF and noted that growth was stunted during the first year of life followed by catch-up growth to age 5 years at which time linear growth was approximately normal and proceeded normally until the completion of the study at 8 years of age. Beker and colleagues (2001) substantiated these findings observing that individuals diagnosed with CF during infancy took up to 4 years to attain normal growth.

A study evaluating the nutritional status, pulmonary function, and blood gas concentrations of 673 patients with CF found that patients with weight-for-height values below the 70^{th} percentile had a two-year mortality rate of greater than 50% (Kerem et al. 1992). Another study evaluated the effects of malnutrition and nutrition-related growth stunting on muscle catabolism and body composition in nine malnourished pediatric CF subjects and 8 controls by determining urinary creatinine excretion, creatinine height index, urinary 3-methylhistinine, whole body potassium, and anthropometric measurements. The CF subjects had significantly lower ($p<0.005$) muscle mass compared to the controls.

Furthermore, the mean rate of muscle protein catabolism and the mean 3-methylhistidine concentrations were higher in the CF subjects compared to controls. The investigators concluded that growth stunting in CF children is due to a decline in "protein energy" similar to that of protein energy malnutrition, but with a much higher catabolism of muscle protein (Miller et al. 1982). These studies suggest the need for aggressive nutrition intervention in underweight CF children to prevent further wasting and increased mortality.

Nutritional supplementation can be used to help restore the growth rate to a normal level in patients with growth deficits secondary to malnutrition (Gaskin 1988). Improvement in the nutritional status of individuals with CF has occurred over the past two decades. Richardson et al. (2000) collected anthropometric data and 7-day food intake diaries from a group of 43 CF subjects and compared them to data obtained in 1983 using the same protocol from 44 different subjects with CF. It was observed that the incidence of malnutrition, as defined by a BMI <20, was 62% in 1983, and only 9% in 2000. Furthermore, the percentage of body fat and energy intake increased significantly in male and female CF patients. Overall, males and females showed a significant increase in weight, height, and body mass index. Despite apparent improvements in growth over the past 2 decades, a recent study consisting of 34 CF children ages 6-11 years showed that CF children still lag behind the National Center for Health Statistics reference population in height and weight for age and gender categories (Stapleton et al. 2001).

Pulmonary Function and Nutrition

Research indicates a correlation between malnutrition and decreased pulmonary function. A study by Ramsey and colleagues (1992) showed that anorexia, an elevated metabolic rate, and subsequently, elevated energy requirements, are associated with chronic pulmonary infections. One such microorganism responsible for chronic pulmonary infections is *Pseudomonas aeruginosa* (Stallings et al 1994). Malnutrition also contributes to a decline in pulmonary muscle function, ventilatory drive, and immune function (Dalzell et al. 1992, Shepherd et al. 1980). CF patients with chronic pulmonary disease have an increase in protein catabolism, which further increases the need for adequate nutrient intake (Dodge 1988). Pulmonary exacerbations also may contribute to anorexia in individuals with CF secondary to associated nausea and vomiting and a general feeling of poor health (Stallings et al.1994).

Studies suggest that the severity of respiratory disease in patients with CF is related to changes in body composition. CF subjects with moderate to severe nutritional depletion and lung disease have a 25-80% larger energy requirement than matched non-CF subjects. The acute phase immune response is practically continuous in CF patients; thus, it is thought that catabolism is increased by interleukins-1 and –6, tumor necrosis factor alpha (TNF-α), and counterregulatory hormones. It also is presumed that an increase in the immune response mobilizes skeletal muscle and fat stores for use as backup energy sources, making adequate nutrition a necessity for replenishing energy stores (Ionescu et al. 2002).

The effect of poor pulmonary function and chronic inflammation on body composition was evaluated in a study of 40 adult CF patients and 22 healthy controls (Ionescu et al 2002). It was observed that CF patients had increased excretion of psuedouridine (PSU), a protein breakdown marker, and increased excretion of N-telopeptides of type I collagen (NTx), a bone connective tissue breakdown marker. These markers were related to low fat-free mass and bone mineral density. In addition, PSU was inversely associated with $FEV_{1.}$ These investigators suggested that low fat-free mass and bone mineral density were associated with pulmonary inflammation and disease, suggesting an increase in protein utilization as an energy source due to the increased excretion of PSU. A possible explanation for lack of use of fat stores as an energy source is that "futile cycling" between the liver and fat stores may be occurring. The inflammatory mediators, TNF-α and interleukin-6, were elevated in CF patients and correlated with PSU and NTx. Cytokines may impair use of lipid stores since they are involved in stimulating peripheral lipolysis and hepatic lipogenesis (Ionescu et al. 2002).

Nutrient Malabsorption

Pancreatic insufficiency associated with CF contributes to maldigestion and malabsorption of fat and protein. Normally, most digestion and absorption occurs in the upper small intestine. However, low levels of lipase and colipase, as well as decreased bicarbonate secretion, minimize digestion and subsequent absorption of fat and protein (Lankisch & DiMagno 1999). Fat malabsorption causes a loss of fat-soluble vitamins, essential fatty acids, and calories.

Steatorrhea can contribute to a reduction in bile salts and bile acids, which exacerbates malabsorption. According to Ramsey et al. (1992), CF individuals with pancreatic insufficiency, steatorrhea, and malnutrition have poorer growth, pulmonary function, and long-term survival prognosis compared to individuals without pancreatic insufficiency.

Medical Management of Cystic Fibrosis

Managing CF is very complex and is accomplished by using physical therapy, antibiotic treatment, medications, nutrition supplementation, and possibly lung transplantation. While treatments are available to help control the progression of the disease, none of them completely eliminate the signs and symptoms of CF. Managing the disease requires aggressive and continuous therapy by the patient and the patient's family including chest physical therapy, antibiotic therapy, bronchodilators, mucolytics, corticosteroids, possible supplemental oxygen, and nutrition therapy that may include supplementation and/or alternate feeding modalities. When these methods of therapy fail, lung transplantation is a final option for managing CF.

Chest Physical Therapy

Chest physical therapy or postural drainage ideally is conducted twice daily to loosen viscous mucus in the respiratory tract. Palpation forces mucus into the central airways allowing it to be coughed up, thereby facilitating easier breathing. Equipment used to assist with physical therapy includes: mechanical percussors/vibrators, percussor vests, percussor packs, *Flutter* valves, and postural drainage tables (Orenstein 1997, Shale 1996).

Antibiotic Therapy

The choice of antibiotic regimen is determined from routine sputum cultures and/or throat swabs. Due to slow antibiotic responses in patients with CF, antibiotics are administered orally at high doses for 10-14 days. Alternatively, antibiotics can be given intravenously in patients diagnosed with allergies or bacterial sensitivities. Individuals with moderate to severe lung disease may receive antibiotic therapy (i.e., gentamicin, colomycin, or tobramycin) via a nebulizer. Nebulized antibiotic treatment is typically given following physical therapy twice daily (Shale 1996).

Bronchodilators

Bronchodilator medications are necessary to expand the obstructed bronchi and ease expectoration of mucus when asthma develops in conjunction with CF. Bronchodilators can be taken orally, inhaled as an aerosol using a nebulizer, or injected. Some beta-adrenergic medications, such as albuterol, can be inhaled as an aerosol or taken orally. Side effects of these beta-antagonists include increased heartbeat, hyperactivity, and shakiness. Theophyllines are weaker oral bronchodilators that can be taken as a capsule, liquid, or tablet in short-acting or slow-release forms. Side effects associated with theophylline usage are upset stomach, loss of appetite, or vomiting (Orenstein 1997).

Mucolytics

Mucolytics, such as nebulised n-acetylcysteine, are administered to increase expectoration of dense sputum (Shale 1996). Another mucolytic called DNase, or Pulmozyme™, is used to catabolize the DNA released from white blood cells that becomes incorporated in the pulmonary mucus making it more

adherent to the respiratory tract. This drug appears to benefit some patients with CF resulting in a 5% enhancement of lung function when used once a day (Orenstein 1997).

Corticosteroids

CF patients with acute asthma or allergic bronchopulmonary aspergillosis may be treated with oral prednisolone to decrease bronchi inflammation and constriction (Orenstein 1997, Shale 1996). Proposed modes of action include inhibition of chemotaxin release or inhibition of neutrophil synthesis and activation (Kennedy 2001). Corticosteroids can be administered orally, by inhalation, or by intravenous injection (Orenstein 1997). Treatment with corticosteroids often does not directly benefit patients with CF, but may improve their overall sense of well-being. Diabetes is a common side effect associated with this form of treatment (Shale 1996). Other side effects include increased appetite, acne, decreased rate of linear growth, and immunosuppression (Orenstein 1997).

Oxygen

CF patients with severe lung disease may suffer from hypoxemia, which can necessitate the use of oxygen therapy (Shale 1996). Oxygen can be stored either as liquid or gaseous oxygen and is usually administered via a nasal cannula or mask. The amount of oxygen administered is determined based on a blood gas concentration or pulse oximetry (Orenstein 1997).

Lung Transplantation

Lung transplantation is an option available to CF patients with severe lung disease characterized by a lung capacity at or below 25-30% of the normal level

and a high concentration of carbon dioxide in the blood. Lungs from a healthy donor are placed in an individual with CF to relieve the pulmonary impairment associated with the dysfunctional CFTR, but the transplant does not cure the disease since it does not directly alter the functioning of other organ systems. The main difficulty with transplantation is the possibility of rejection of the donated lung. Therefore, individuals who have undergone a lung transplant are required to take immunosuppressive drugs to prevent rejection, as well as steroids to decrease inflammation of the tissues (Hopkin 1998). The current 3-year survival rate for CF lung transplant patients is approximately 60%, making it a very dangerous operation with serious risks (Ratjen & Doring 2003).

Gene Therapy

In the early 1990s, research using recombinant adenoviruses to correct CFTR mutations was initiated with the goal of finding a cure for CF (Driskell & Engelhardt 2003). Since this time, numerous extracellular and intracellular barriers have been identified and studied. Problems related to the impact on innate and acquired immune function also have been posed. Currently, there is no approved gene therapy for individuals with CF; however, studies are still pending. Research is being conducted using recombinant viruses with cDNA in their genome and synthetic vectors attached to plasmid DNA. Short duration of gene expression is problematic, thereby requiring repeated gene transfer vector (GTA) treatment, which is inhibited by neutralizing antibodies. In the future, a longer lasting GTA or an antibody resistant GTA will likely be identified (Ferrari et al. 2003).

Enzyme Replacement Therapy

To improve digestion and absorption, acid-resistant pancreatic enzyme replacement products were developed in the late 1980s to be taken by individuals with CF at every meal and snack (Borowitz et al. 2002, Lankisch & DiMagno 1999). Stool patterns, appetite, and growth curves are used to determine the appropriateness of enzyme dosages. However, a 72-hour fecal fat test is considered the most accurate test of fat absorption (Borowitz et al. 2002).

Supplemental enterically-coated pancreatic enzymes contain amylase, protease, and lipase. The effectiveness of pancreatic enzyme replacement therapy is influenced by the pH of the duodenum. The enteric coating of pancreatic replacement enzymes are designed to dissolve in the alkaline pH of the duodenum. However, increased gastric acid along with decreased pancreatic bicarbonate production can delay removal of the enzyme coating thereby decreasing nutrient absorption (Orenstein 1997). Histmine-2 receptor blockers or proton pump inhibitors may alleviate this problem; however, response is variable (Francisco et al. 2002). Enzyme dosage is determined on an individual basis. Enzyme dosing should not exceed 2500 lipase units/kg/meal or 4000 lipase units/gram of fat/day to avoid a serious intestinal complication known as fibrosing colonopathy (Borowitz et al. 2002, Orenstein 1997). The initial level of pancreatic enzymes prescribed for patients with CF one year of age and older is 500 units of lipase/kg body weight/meal and 250 units of lipase/kg body weight/snack. This dose is adjusted every 3-4 days until a normal stool pattern is observed (Hodson & Geddes 2000).

Commonly prescribed enzyme products include Creon™, Pancrease™, and Ultrase™ (Samour et al. 1999). Generic enzymes are not bioequivalent to proprietary enzymes and should not be administered (Hendeles et al. 1990). Furthermore, enzymes that are exposed to heat, chewed or crushed, or exposed to alkaline foods for an extended period of time lose their effectiveness due to denaturation (Borowitz et al. 2002).

Nutritional Management of Cystic Fibrosis

Exacerbated coughing and dyspnea in individuals with CF contributes to an increase in resting energy expenditure (REE). Prior to 1970, a low-fat, high-carbohydrate diet was recommended for CF patients with the idea that it would decrease symptoms associated with fat maldigestion and malabsorption. However, in the early 1970s, it was determined that a high-fat diet providing 40% of the kilocalories from fat and supplemented with pancreatic enzymes is beneficial since fat has a higher caloric density in comparison to carbohydrates (Pencharz 1983, Richardson et al. 2000). Furthermore, a high-fat diet is more efficient because 15% of kilocalories derived from carbohydrate sources are used to convert carbohydrates into fat sources (Pencharz 1983). In addition, a low-fat diet is limited in fat-soluble vitamins and essential fatty acids (EFA), which decreases the amount of prostaglandin precursors and can result in changes in cell membrane integrity (Burdge et al. 1994, Rivers & Hassam 1975). A classic study by Corey and colleagues (1988) comparing the survival, growth, and pulmonary function of CF patients in Boston and Toronto illustrates the advantage of this dietary change. In the early 1970s, a high fat, high calorie diet

that included ingestion of 20-30 pancreatic enzyme capsules per meal was recommended for patients seen at a CF clinic in Toronto. In contrast, a CF clinic in Boston recommended a low fat, high calorie diet with minimal use of pancreatic enzyme replacement therapy. Height, weight, age, sex, and pulmonary function were recorded during clinic visits at each institution and the data were compared. Results showed that the Toronto survival curve was higher than the Boston curve beyond 10 years of age. The median age of survival in Boston was 21 years, but 30 years in Toronto. In addition, Toronto patients were significantly taller than Boston patients and Toronto male patients maintained a significantly higher weight than the Boston male patients. Overall, this change in dietary management resulted in increased growth and energy consumption in CF patients (Pencharz 1983). Thus, it is recommended that CF individuals consume a minimum of 120% of the recommended dietary allowance (RDA) for energy based on age and gender, with approximately 40% of the calories as fat (Gaskin 1998, Navarro et al. 1995).

Fat Intake and Utilization

Use of enzyme replacement therapy is necessary for pancreatic insufficient CF individuals to improve fat absorption. Burdge et al. (1994) examined the effects of a high-fat diet with enzyme supplementation in 26 patients with CF compared to a group of 15 control subjects. They reported adequate fat absorption relative to the amount absorbed by the non-CF individuals, as evidenced by normal concentrations of plasma phosphatidlycholine (PC), triacylglycerol (TG), and cholesterol and no "clinically significant EFA deficiency." This observation indicates that CF individuals taking enzyme replacement

therapy actually absorb adequate amounts of dietary fat compared to non-CF individuals despite the fact that fat malabsorption still occurs. These researchers concluded that the current dietary management of CF patients with a high-fat diet and enzyme replacement therapy results in normal concentrations of plasma lipids.

Additional gastrointestinal disorders, such as decreased motility, disturbed acid-base balance, and hepatobiliary disease prevent complete restoration of normal digestion with enzyme replacement therapy (Lankisch & DiMagno 1999). To address the issue of fat malabsorption, Kalivianakis and colleagues (1999) studied 10 pediatric CF patients receiving pancreatic enzyme replacement therapy. Total fat absorption was <96% for the group, and 8 out of 10 subjects had a fecal fat excretion >6 g/d, indicating fat malabsorption. No correlation was observed between fat intake per kilogram body weight and the percentage of total fat absorption. Thus, a high fat intake was not responsible for fat malabsorption. In addition, there was no correlation between the quantity of supplemented lipase enzymes, which ranged from 460 to 1820 IU/g fat ingested, and the percentage of absorbed total fat. However, following [^{13}C] linoleic acid (LA) ingestion, there was a correlation between total fat absorption and 8-hour plasma [^{13}C] LA concentrations. It was concluded that long-chain fatty acid uptake in the intestine was incomplete. A possible explanation for this correlation is that the mucus secretions associated with CF may limit translocation of long-chain fatty acids across the intestinal epithelium by altering the intestinal "unstirred water layer" thickness. Overall, it was determined that a decrease in

mucosal uptake or inefficient intraluminal solubilization of long-chain fatty acids is responsible for fat malabsorption in patients with CF who take enzyme supplements.

Fat-soluble Vitamins

Due to fat malabsorption, CF patients with pancreatic insufficiency require supplementation with the fat-soluble vitamins A, D, E, and K (Shale 1996). Vitamin K deficiency is particularly problematic during infancy or secondary to a reduction of the intraluminal bile salt pool in patients with CF-associated liver disease (CFLD) (Ramsey et al. 1992, Wilson et al. 2000). A study designed to treat vitamin K deficiency with a combination of fat-soluble vitamins, ADEK™, showed that daily supplementation decreased the concentration of prothrombin in vitamin K absence (PIVKA-II), thus reducing the amount of decarboxylated prothrombin and halving the incidence of biochemical vitamin K deficiency (Wilson et al. 2000). This finding is important because it illustrates the need for routine fat-soluble vitamin supplementation, especially with vitamin K, in patients with CF. Supplemental vitamin A is necessary for immunity, epithelial growth, and vision. Individuals with CF who have pancreatic insufficiency may be at risk for becoming vitamin A deficient since pancreatic lipase is needed to metabolize retinyl esters for absorption. Vitamins D and E also are needed for bone health and antioxidant activity, respectively (Borowitz et al. 2002). A study examining fat-soluble vitamin deficiency in 96 patients with CF aged 4-8 weeks old found that 45.8% had deficient levels of one or more fat-soluble vitamins. Over a 10-year period, the rate of deficiencies of vitamins A, D, and E were reported as

11.1%, 12.5%, and 57.1%, respectively, at one or more times regardless of vitamin supplementation. The group of patients who were vitamin sufficient at baseline developed deficiencies of vitamins A, D, or E one or more times at a rate of 4.5%, 14.4%, or 11.8%, respectively. It is suggested that this problem could be due to inefficient micellar solubilization initiated by a reduction in bile acid pool size and intraluminal bile acid concentration (Feranchak et al. 1999).

Gastrostomy Tube Feeding in Cystic Fibrosis

Tube feeding is one option available to practitioners when caloric requirements are not met by oral feeding (Marin et al. 1994). These feedings are typically administered nocturnally through a nasogastric, gastrostomy tube (GT), or percutaneous endoscopic gastrostomy (PEG) tube (Navarro et al. 1995). A variety of formulas are available for tube feeding including whole protein, semi-elemental, and elemental preparations (Lees & Smyth 2000). It is thought that tube feeding may improve weight gain, growth and nutritional status. Furthermore, it has been suggested that tube feeding may improve or stabilize pulmonary function and improve body image, thus improving the quality of life (Navarro et al. 1995). Initially, it is recommended that tube feedings provide 30-50% of the estimated energy requirements with subsequent adjustments based on change in weight and height (Borowitz et al. 2002).

A comparison of 10 undernourished CF patients ages 3 to 13.2 years receiving a nocturnal semi-elemental high-nitrogen formula and 14 FEV_1 -, sex, and height-matched controls receiving standard care showed that those patients receiving supplementation experienced catch-up weight gain, increased height, and fewer annual pulmonary infections compared to their initial infection rates.

These researchers also reported that deterioration in lung function was significantly reduced with supplementation. In addition, it was observed that 6 to 12 months of nocturnal feedings was associated with a reduction in the rate of catabolism and stabilization of anabolism, thus demonstrating improvement in overall nutritional status (Shepherd et al. 1986). A 5-year follow-up study of the same patient population showed that at years 4 and 5 post-supplementation, the study group had a better weight to height gain than the control group. The study group also had a lower mortality rate than the control group. FEV_1 decreased significantly in the control group 3 years post-supplementation; however, the decline in pulmonary function between the study group and the control group was the same 5 years post-supplementation, thus suggesting that continued supplementation is needed to maintain positive pulmonary benefits (Dalzell et al. 1992).

The benefit of continued supplementation was substantiated in another study with 8 pediatric CF patients experiencing growth failure. Nutrition support was provided to these patients for 3 months using nocturnal tube feedings of an elemental solution. A significant increase in weight and height, but no significant alteration in anthropometric measurements such as triceps skinfold or biochemical measurements like serum albumin, were noted. Three months post-supplementation, however, it appeared that the youngest patients benefited the most from supplementation in terms of their height compared to the older patients. At the time of supplementation cessation, the rate in linear growth for all study subjects had reached normal levels for age, thus indicating a plateau

effect. Following supplement termination, patients with severe lung disease did not maintain improvements in weight or the linear growth rate observed with supplementation (Moore et al. 1986).

O'Loughlin et al. examined the response to nocturnal nasogastric tube feeding in 8 malnourished (i.e., IBW 77.6%) CF patients with severe pulmonary dysfunction by comparing weight, height, pulmonary function, and patient well being. Nasogastric nocturnal supplementation resulted in weight gain, but did not alter pulmonary status likely to be secondary to the damage already inflicted. Patient well being, as measured by dyspnea, activity level, and attendance at school/work, was improved in 7 out of 8 patients following supplemental tube feeding (O'Loughlin et al. 1986).

Vaisman and colleagues (1991) examined the effect of supplemental GT feedings on protein turnover and REE in patients with CF. In this study, 8 undernourished CF patients (i.e., <85% ideal weight for height) ages 13.8 to 21.8 years and 20 normal controls were evaluated pretreatment, 2 to 3 months after GT placement, and one-year post-GT placement. No significant change in height, pulmonary function, or protein turnover was observed at one-year post-GT placement compared to pretreatment. Furthermore, the ratio of protein synthesis to REE was not significantly different one year post-GT feeding. Although the REE was elevated after supplementation, it could not be attributed to protein synthesis, suggesting that an unidentified genetic component of CF may increase REE (Vaisman et al. 1991).

Marin et al. (1994) evaluated the safety and efficacy of PEG tubes for providing nutrition support in a retrospective study of 70 children ages 3 months to 24 years, 13 of whom had CF. Subjects' weights were obtained prior to PEG placement and follow up information was gathered from medical records, healthcare facilities, and patient contact 6 months post PEG placement. They reported that patients with CF or congenital heart disease had the most significant increase in weight (i.e., 80% and 85%, respectively). These findings suggest that GT feeding is a particularly effective form of nutrition supplementation in pediatric patients with CF (Marin et al. 1994).

Based on a study by Steinkamp and von der Hardt (1994), it appears that significant weight gain occurs during the first 3-6 months of GT feeding, after which weight gain plateaus. In this study, 14 CF patients (7 to 23 years) with PEG tubes gained approximately 1 kg/mo during the first 6 months of feeding via a PEG, but the rate of weight gain slowed in subsequent months. Weight gain was attributed to increases in body fat, as well as fat free mass, and pulmonary function was stabilized in all but one subject at the one year follow up visit. However, the majority of the subjects had advanced lung disease at the beginning of the study, therefore, implying that stabilization in pulmonary function may be a natural phenomenon since further decline would have resulted in mortality (Steinkamp & von der Hardt 1994).

Nutritional outcome after tube placement has been reported to be directly related to lung function when the FEV_1 is below 40% of the predicted value prior to tube placement (Walker & Gozal 1998). Williams et al. (1999) reported that

GT feeding in severely malnourished patients (i.e., BMI <17 kg/m^2) resulted in a significant increase in nutritional status and stabilization of pulmonary function in those patients with advanced pulmonary disease. Despite the impact of this intervention on weight gain, mean BMI was still below normal (<20 kg/m^2). Although these researchers reported stabilization of pulmonary function, it should be noted that the subjects in this trial had severe pulmonary dysfunction, which can stabilize for years without any nutritional intervention (Gaskin 1988).

Research Significance

Reports of the success of supplemental tube feeding in individuals with CF are variable, ranging from increases in weight, height, and pulmonary function to no observed difference after tube feeding. Conflicting research findings may account for the lack of agreement regarding the benefit(s) of supplemental GT feeding and the lack of practice standards defining the most appropriate time to initiate GT feeding, if any, for patients with CF. Variables that may account for differences in research outcomes include small sample size, the severity of lung disease, type of formula administered, and duration of GT feeding. Increases in weight gain were not always clinically relevant and stabilization of pulmonary function could not be attributed to supplementation (Gaskin 1988, O'Loughlin et al. 1986). The majority of these studies did not observe the effect of tube feeding on the number of hospitalizations, which would be beneficial in evaluating if tube feeding decreases the number of CF exacerbations requiring hospitalization and for determining if tube feeding is more economical than standard nutrition care in malnourished individuals with CF. It is possible that earlier introduction of GT

feeding would produce clinically significant outcomes, a variable that warrants further investigation.

To investigate the potential relationship between the timing of initiation of GT feedings, nutritional status, pulmonary function, and survival data were collected from the medical records of CF patients with moderate to severe lung disease who received care from the UF College of Medicine Pediatric Pulmonary Division. It was hypothesized that the timing of GT feeding initiation would influence survival outcomes for individuals with CF.

CHAPTER 3
MATERIALS AND METHODS

Subject Description and Study Design

This study was a retrospective chart review of subjects with CF who received care at the University of Florida College of Medicine Pediatric Pulmonary Center between 1990-2002. The University of Florida Health Science Center Institutional Review Board (IRB) approved the study protocol, which included a provision to obtain data from medical records of patients who were consented previously under IRB protocol #324-97. Data were collected from the medical records of subjects who had a GT placed at the time of or prior to initiation of IRB protocol #324-97, but who were consented once that study began. Subjects who had their GT placed prior to IRB protocol #324-97 received two copies of a consent letter, as well as a self-addressed stamped envelope, and were contacted via telephone regarding their willingness to allow their data to be used for the present study. Those individuals who wished to participate in the study returned the signed consent letter to the Pediatric Pulmonary Center. All other subjects received a letter informing them of this study and requesting that they contact the principal investigator in the event that they did not wish to participate. Letters were not sent to the families of deceased subjects.

The inclusion criteria for this study were as follows: diagnosis of CF, $\leq$ 30 years of age at the time of GT placement, and initiation of GT feeding prior to April 15, 2002 for the purpose of providing supplemental nutrition support for a

minimum of six months or until the time of death. Subjects receiving lung transplants were excluded from the study. Subjects alive at the time of data analysis were classified as survivors, while deceased subjects were classified as non-survivors.

Data for subjects were obtained from the CF patient database, Pediatric Pulmonary Center medical records, and Shands Hospital medical records for the period of time extending 12 months prior to and following GT feeding initiation. The data collected included weight, height, actual and percent predicted FEV_1, $FEF_{25-75\%}$ and FVC, type of insurance (i.e., private insurance, Medicaid and/or Children's Medical Services), and number of days hospitalized 12 months prior to and following GT feedings. BMI was calculated from measures of weight and height (i.e., kilograms of body weight divided by height in meters squared) at the time of GT feeding initiation. Descriptive data including age, gender, date of birth, date of GT placement and removal (if applicable), and date of expiration (if applicable) also were collected. All data were key coded and kept in a locked file to prevent a breach of subject confidentiality.

Statistical Analysis

All statistical analyses were conducted using SAS version 8.02 (SAS Institute 2001). Mean age, weight, height, FEV_1, $FEF_{25-75\%}$ and FVC were calculated for all subjects and by gender and survival status. The mean age at GT feeding initiation and duration of GT feeding also was calculated for survivors and non-survivors in whom gastrostomy tubes had been removed prior to April 2002.

Rate of Change Comparisons

The Shapiro-Wilk test was used to test for normality of the weight, FEV_1, FVC, and $FEF_{25-75\%}$ data. All variables were non-normal, so the Signed Rank test was used to compare the difference between the rate of change for weight, FEV_1, FVC, and $FEF_{25-75\%}$ pre- and post-GT feeding.

Comparison of Number of Days Hospitalized per Month

The one-sample t-test was used to compare the difference in the number of days hospitalized per month 12 months pre- and post-GT feeding since the data were normal as determined from the Shapiro-Wilk test.

Relation of Insurance Type to Number of Days Hospitalized per Month

To determine if the type of insurance affected the number of days hospitalized per month, two different statistical analyses were conducted, one was a nonparametric test and the other was a test for normal data. The Wilcoxon test, a nonparametric test, was conducted to compare private (n=3) and public (n=15) insurance data 12 months prior to GT placement and 12 months following GT feeding. For the parametric analysis, the Shapiro-Wilk test revealed the data to be normal; therefore, a two-sided, two-sample t-test using pooled data was conducted to test for significance. Pooled data for this analysis were used since variances were shown to be equal by a test of variance equality.

Survival Data

Average ($\pm$ standard deviation) BMI, FEV_1, $FEF_{25-75\%}$, and FVC were calculated for survivors compared to non-survivors and males compared to females. To evaluate the differences in pulmonary function and BMI between

survivors and non-survivors at the time of GT feeding initiation, a two-sample t-test using pooled data was administered.

To investigate the optimal time for GT placement to improve survival while controlling for gender and BMI a Survival Analysis was performed using the Cox Regression Model (Cox & Oakes 1984) with a binary variable defined as >40% predicted FEV_1 in comparison to <40% FEV_1. The same analysis was conducted for greater than or less than 30% FEV_1. Hazard ratios for the independent dichotomous variable FEV_1 with 95% confidence limits and estimated p-values were reported. To evaluate the relationship of gender on survival, the Cox Regression Model was administered controlling for the continuous variables FEV_1, $FEF_{25-75\%}$, and FVC and BMI. Hazard ratios with 95% confidence limits and estimated p-values were reported.

CHAPTER 4
RESULTS

Subjects

Twenty-one subjects (i.e., 12 females and 9 males) met the inclusion criteria for this study. The average age of the females at the time of GT placement was 11.6 years, and the average age of the males was 12.3 years. When subjects were divided according to survival, there were 11 survivors (i.e., 6 females and 5 males) and 10 non-survivors (i.e., 6 females and 4 males). The duration of GT feeding for subjects whose gastrostomy tubes had been removed prior to April 2002 was 36.7 months and 14.9 months for survivors and non-survivors, respectively. The average age of non-survivors at the time of death was 15.5 years, while the average age of survivors as of April 2003 was 15.8 years.

Change in Weight, Height, and Pulmonary Function Pre- and Post-GT Feeding Initiation

The mean rate of change in weight, height, and PFTs pre- and post-GT feeding initiation suggests an overall trend toward improvement since the rate of change in these variables improved post-GT feeding initiation compared with the pre-GT rate of change (Table 1).

The Signed Rank test was used to compare the rate of change for weight, height, $FEV_{1,}$ $FEF_{25-75\%,}$ and FVC pre- and post- initiation of GT feeding since the Shapiro-Wilk test revealed the data to be non-normal. Analysis of the rate of

change for each variable pre- and post-GT feeding initiation (Table 1) indicated that only $FEF_{25-75\%}$ improved significantly ($p = 0.0006$) following GT placement.

Table 1. Comparison between rate of change pre- and post- GT feeding initiation for weight, height, and PFTs

Response Variable	n	Rate*	p-value
Weight pre-GT	16	-0.15 ± 0.58	0.9102
Weight post-GT	15	-0.05 ± 0.11	
Height pre-GT	17	0.42 ± 0.72	0.5416
Height post-GT	16	0.34 ± 0.30	
FEV_1 pre-GT	17	0.00 ± 0.04	0.2435
FEV_1 post-GT	17	0.01 ± 0.03	
$FEF_{25-75\%}$ pre-GT	16	-0.03 ± 0.03	0.0006
$FEF_{25-75\%}$ post-GT	16	0.03 ± 0.05	
FVC pre-GT	17	0.01 ± 0.06	0.7467
FVC post-GT	17	0.01 ± 0.05	

*Values represent mean ± standard deviation

Comparison Between Days Hospitalized per Month Pre- and Post-GT Feeding Initiation and by Type of Insurance

No significant difference was detected in the average number of days hospitalized per month secondary to CF complications pre- (2.6 ± 2.0 days) and post- (2.6 ± 1.9 days) GT feeding initiation (Table 2). When the number of days hospitalized per month were compared according to private versus public insurance, patients with public insurance (n=15) spent a mean of 2.7 ± 2.0 days per month in the hospital prior to GT placement and 2.5 ± 1.8 days following GT feeding, whereas subjects with private insurance (n=3) spent a mean of 1.2 ± 1.1 days per month hospitalized prior to GT placement and 3.2 ± 3.0 days per month

post-GT feeding (Table 2). No significant differences were detected in the number of days hospitalized pre- or post-GT feeding initiation based on type of insurance.

Table 2. Comparison of number of days hospitalized per month pre- and post-GT feeding for all subjects and by insurance type (i.e., public vs private)

Time frame and type of insurance	n	Number of Days Hospitalized*	p-value
Pre-GT	19	2.6 ± 2.0	0.9051
Post-GT	19	2.6 ± 1.9	
Pre-GT (public insurance)	15	2.7 ± 2.0	0.2216†
Pre-GT (private insurance)	3	1.2 ± 1.1	
Post-GT (public insurance)	15	2.5 ± 1.8	0.5527‡
Post-GT (private insurance)	3	3.2 ± 3.0	

* Values represent mean ± standard deviation
† degrees of freedom = 16; t-value = 1.27
‡ degrees of freedom = 16; t-value = -0.61

Comparison of BMI and Lung Function in Survivors versus Non-survivors

The mean BMI and PFT values for survivors and non-survivors are shown in Table 3. Percent-predicted values for FEV_1, $FEF_{25-75\%}$, and FVC were significantly higher in survivors compared to non-survivors at the time of GT placement (Figure 1). No significant difference was detected between survivors and non-survivors for BMI.

Table 3. Comparison of BMI and lung function at GT placement in survivors versus non-survivors

	BMI† (n=9)	FEV_1†‡ (n=6)	$FEF_{25-75\%}$†‡ (n=6)	FVC†‡ (n=6)
Survivors	14.5±1.3	55.2±14.6	25.2±9.8	74.8±17.2
Non-survivors	14.1±1.8	29.8±12.2	10.9±6.2	46.3±19.5
p-value	0.5340	0.0086	0.0130	0.0228
Degrees of freedom	16	10	10	10
t-value	0.64	3.26	3.02	2.69

† Values represent mean ± standard deviation
‡ Values reported as percent predicted

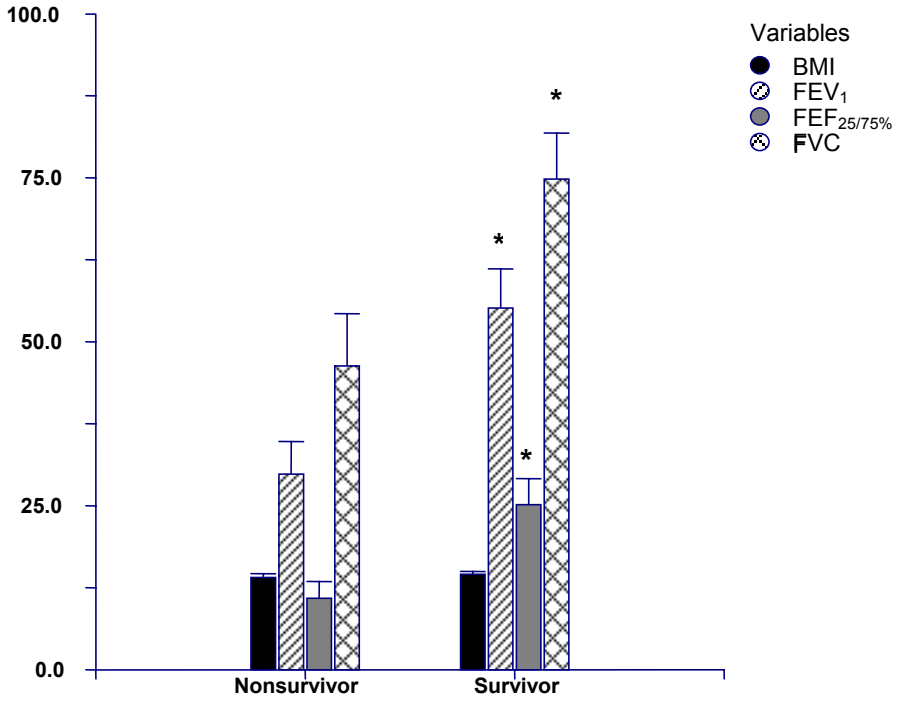

Figure 1. BMI and lung function of survivors vs non-survivors at GT placement

* Denotes significant difference between survivors and non-survivors for the percent predicted response variables FEV_1 p = 0.0086, $FEF_{25-75\%}$ p = 0.0130, FVC p = 0.0228

The mean BMI and PFT values for males versus females according to survival status (i.e., survivor or non-survivor) are presented in Tables 4 and 5, respectively. These data also are depicted in Figures 2 and 3.

Table 4. BMI and lung function by gender at GT placement (survivors)

	BMI†	**FEV_1**†‡	**$FEF_{25-75\%}$**†‡	**FVC**†‡
Males	14.7 ± 1.2 (n=5)	52.0 ± 13.9 (n=3)	22.0 ± 5.6 (n=3)	74.0 ± 21.7 (n=3)
Females	14.3 ± 1.7 (n=4)	58.3 ± 17.7 (n=3)	28.3 ± 13.3 (n=3)	75.7 ± 16.3 (n=3)

† Values represent mean ± standard deviation
‡ Values reported as percent predicted

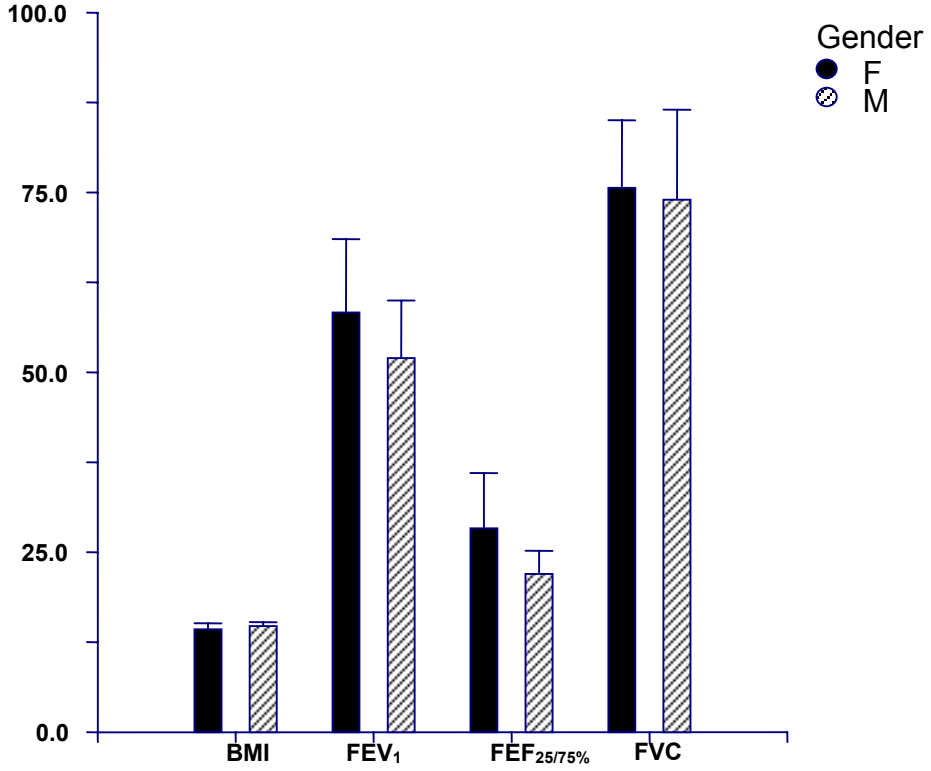

Figure 2. BMI and lung function at GT placement by gender (survivors)

Measurements of lung function reported as percent predicted

Table 5. BMI and lung function by gender at GT placement (non-survivors)

	BMI†	**FEV_1**†‡	**$FEF_{25-75\%}$**†‡	**FVC**†‡
Males	13.5 ± 0.5 (n=4)	20.5 ± 9.2 (n=2)	8.3 ± 3.9 (n=2)	30.5 ± 7.8 (n=2)
Females	14.5 ± 2.3 (n=5)	34.5 ± 11.5 (n=4)	12.3 ± 7.2 (n=4)	54.3 ± 19 (n=4)

† Values represent mean ± standard deviation

‡ Values reported as percent predicted

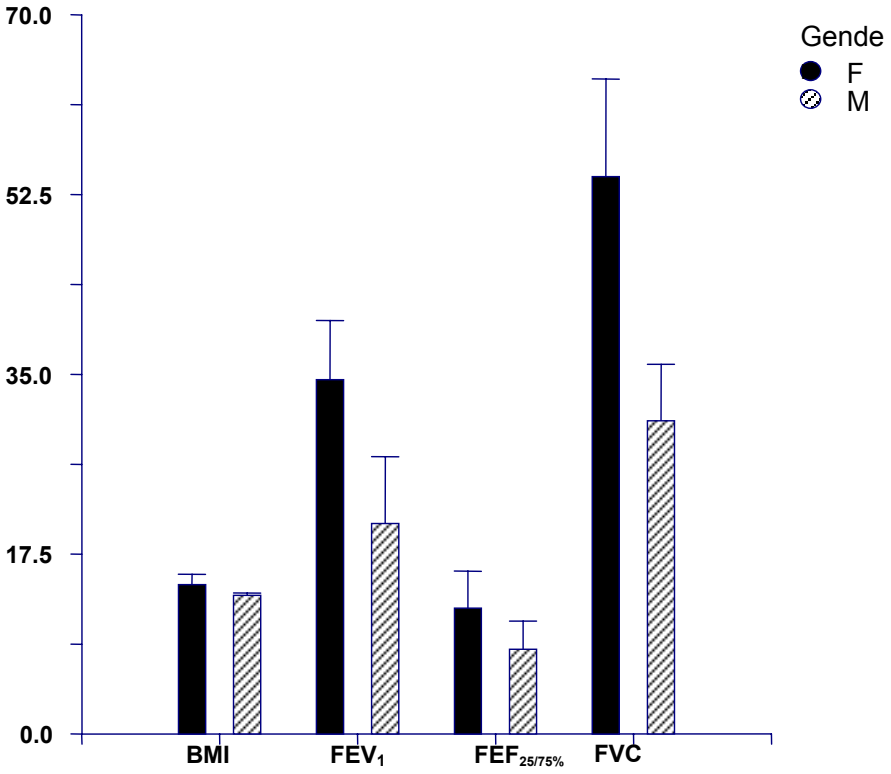

Figure 3. BMI and lung function at GT placement by gender (non-survivors)

Measurements of lung function reported as percent predicted

The Effect of Gender on Survival

The Cox Regression Model including hazard ratios, 95% confidence limits, and p-values was used to evaluate the effect of gender, BMI, and either FEV_1, $FEF_{25-75\%}$, or FVC on survival. For each analysis, females were set as the default since the literature indicates that females traditionally are at a greater mortality risk than males (Zemel et al. 2000). A hazard ratio greater than 1 would be in opposition to the default, suggesting that females have a lower mortality risk than males. All gender hazard ratios were less than 1 for FEV_1 (0.33), $FEF_{25-75\%}$ (0.38) and FEV (0.21) (Table 6), which support the current literature of higher

mortality in females. Hazard ratios were not significant, however, because the confidence limits crossed 1.0 and the p-values were greater than 0.05.

Table 6. Relationship between gender and survival based on lung function

Variables	p-value	Hazard Ratio	95% Confidence Limits
FEV_1			
Gender	0.38	0.33	0.03-3.82
FEV_1	0.66	0.98	0.90-1.07
BMI	0.19	0.63	0.31-1.26
$FEF_{25-75\%}$			
Gender	0.40	0.38	0.04-3.72
$FEF_{25-75\%}$	0.77	0.98	0.85-1.12
BMI	0.11	0.59	0.31-1.13
FVC			
Gender	0.27	0.21	0.01-3.37
FVC	0.31	0.96	0.88-1.04
BMI	0.46	0.77	0.37-1.57

Relationship Between Severity of Lung Disease and Survival

The relationship between severity of lung disease at the time of GT placement and survival was calculated with subjects separated above or below FEV_1 (percent predicted) values of 30 and then 40%. Subjects with FEV_1 percent-predicted values below 40% had two times the mortality risk of subjects with FEV_1 values greater than 40%; however, due to the small sample size this result was not statistically significant (Table 7). When subjects were separated above or below 30% FEV_1, the hazard ratio was 0.29, suggesting that subjects below 30% predicted FEV_1 had a mortality three-fold higher mortality risk than subjects with values greater than 30% (Table 8).

Table 7. Survival based on FEV_1 <40% or >40%

Variables	p-value	Hazard Ratio	95% Confidence Limits
Gender	0.47	0.60	0.15-2.41
FEV_1	0.44	0.42	0.05-3.71
BMI	0.09	0.69	0.45-1.06

Table 8. Survival based on FEV_1 <30% or >30%

Variables	p-value	Hazard Ratio	95% Confidence Limits
Gender	0.26	0.42	0.09-1.92
FEV_1	0.18	0.29	0.05-1.77
BMI	0.22	0.77	0.50-1.18

CHAPTER 5
DISCUSSION AND CONCLUSIONS

Evaluation of Weight, Height, and Pulmonary Changes Pre- and Post-GT Feeding Initiation

Research has reported contradictory results regarding the effect of GT feeding on weight, height, and pulmonary function. Observations from this study indicated that only $FEF_{25-75\%}$ was significantly improved following GT feeding initiation. This finding may not be clinically significant since FEV_1, not $FEF_{25-75\%}$ is considered to be the main indicator of lung function in patients with CF (Cystic Fibrosis Foundation 2002). Despite the observation that there were no observed changes in weight, height, FVC, or FEV_1, there was an overall trend towards improvement. This trend suggests that GT feeding does not significantly improve or worsen weight, linear growth, or pulmonary function. This finding is in opposition to the literature, which tends to support the concept of significant increases in body weight with GT feeding. For example, O'Loughlin et al. (1986), Steinkamp and von der Hardt (1994), and Williams et al. (1999) all reported weight gain with GT feeding. These study discrepancies may be secondary to smaller sample sizes, percentage of calories administered, adherence to regimen, effectiveness of therapies (including pancreatic enzyme therapy) or different tube feeding formulas reported in the literature.

The effect of supplemental nutrition via GT feedings on FEV_1 has been controversial. Similar to Vaisman et al. (1991), this study found no change in

FEV_1. However, other studies, such as the one by Steinkamp and von der Hardt (1994) reported significant improvements. Therefore, the question of the effect of GT feeding on pulmonary function remains debatable. It is not likely that clinically significant improvements in FEV_1 for CF individuals with severe lung disease would occur. It is more probable that stabilization of lung function might occur as lung function declines over time (Gaskin 1988).

GT Feeding and the Number of Days Hospitalized per Month

No significant difference in the number of days hospitalized per month was detected in the study population. This finding suggests that GT feeding does not significantly change the frequency of CF exacerbations. This finding is consistent with the previously mentioned results concerning changes in body weight and pulmonary function. If there were improvements in weight and lung function we would expect a decrease in the frequency of CF exacerbations and therefore, the number of days hospitalized.

Insurance Type and Number of Days Hospitalized per Month

There was no observed relationship between the number of days hospitalized per month and type of healthcare coverage. In this study cohort, subjects presumed to be of lower socioeconomic status (i.e., public insurance) spent an equivalent number of days hospitalized per month secondary to CF as subjects presumed to be of higher socioeconomic status (i.e., private insurance). This finding is in opposition to a study conducted by Schechter and Margolis (1998) that evaluated the number of days hospitalized for Medicaid and non-Medicaid pediatric CF patients receiving care at the University of North Carolina CF Center. Their study noted that Medicaid subjects spent significantly more

days hospitalized and had a higher number of hospitalizations per patient compared to non-Medicaid subjects. One factor that could account for this difference is the degree to which subjects in either group adhered to the medical therapies prescribed. To further address this issue, a prospective study evaluating CF pharmacotherapy adherence using a larger sample of subjects with private insurance should be conducted to determine the role that medical adherence plays in the frequency of hospitalizations.

BMI and Lung Function and Survival Status

BMI and pulmonary function at the time of GT placement were compared between survivors and non-survivors. Survivors had significantly higher pulmonary function values than non-survivors; however, BMI was not significantly different. The mean FEV_1 of survivors was 55% (moderate lung disease), while the mean FEV_1 of non-survivors was 30% (severe lung disease), which corresponds with the eligibility criteria used for lung transplantation (Snell et al. 1998). This finding suggests that earlier initiation of GT feeding based on severity of lung disease may improve survival. Interestingly, no significant difference in mean BMI was detected at the time of GT placement between survivors and non-survivors. Traditionally, weight indices have been the main criterion used to determine when GT feeding should be initiated for optimal health (Borowitz et al. 2002). These study results suggest that FEV_1 values may be an important factor in determining the appropriate time for initiation of GT feeding as a means for improving survival outcome.

Relationship of Gender on Survival

The effect of gender on survival when controlling for pulmonary function and BMI suggests that females are at greater mortality risk than males. Previous studies showed that females had poorer survival compared to males. A study by Zemel et al. (2000) used the CF Foundation National CF Patient Registry data from 1991-1995 to examine changes in weight and height of children with PI between the ages of 5 to 8 years found that females experienced a greater rate of decline in height and weight than males. This observation might have been secondary to pubertal delay commonly observed in females with CF (Johannesson et al. 1997). The decline observed by Zemel et al. (2000) in height and weight was associated with a future decrease in FEV_1 and increased mortality. Analysis of more recent data suggests that males and females have similar survival curves throughout the lifecycle (Cystic Fibrosis Foundation 2002). Our finding of increased mortality in our female cohort after controlling for BMI and pulmonary function suggest that females have an innately increased mortality risk compared to males, a finding that warrants further investigation.

Relationship Between Lung Disease and Survival

In the present study, an FEV_1 level <40% predicted was associated with a two times greater mortality risk compared to an FEV_1 >40%. Furthermore, subjects with an FEV_1 <30% predicted had a three-fold higher mortality risk compared to subjects with an FEV_1 >30%. These findings, in addition to the previous observation that FEV_1 at the time of GT placement is significant for survival, suggest that the timing of GT feeding initiation based on lung disease severity and FEV_1 may be important in improving survival. These results may be

beneficial to healthcare providers when trying to make evidence based decisions such as when to initiate GT feedings for an individual with CF. Gastrostomy tube feeding may be of little or no benefit to the patient if it is initiated once lung function has become severe; however, earlier initiation of GT feeding may prolong survival even in the absence of improvements in BMI.

Future Research

Additional research is needed to substantiate the current study findings and to further determine the appropriate time for GT placement. A large retrospective multicenter study confirming these results could serve as the basis for developing practice standards that benefit patients with CF. A study of this size also would provide the opportunity to develop a predictive model of GT success based on gender, BMI, and lung function. Furthermore, research evaluating the effect of possible confounding variables on survival, such as *Burkholderia Cepacia*, a microbe known to increase morbidity and mortality in CF individuals (Cystic Fibrosis Foundation 1994) and CFRD is needed to eliminate additional variables when evaluating GT feeding success.

LIST OF REFERENCES

Beker, L.T., Russek-Cohen, E., Fink, & R.J. (2001) Stature as a prognostic factor in cystic fibrosis survival. J Am Diet Assoc 101: 438-42.

Bishop, W.P., Haber, B.A., Lichtman, S.N., & Shneider, B.L. (1999) Percutaneous endoscopic gastrostomy feeding improves nutritional status and stabilizes pulmonary function in patients with cystic fibrosis. J Pediatr Gastroenterol Nutr 29: 485-6.

Borowitz, D., Baker, R.D., & Stallings, V. (2002) Consensus report on nutrition for pediatric patients with cystic fibrosis.J Pediatr Gastroenterol Nur 35: 246-59.

Burdge, G.C., Goodale, A.J., Hill, C.M., Halford, P.J., Lambert, E.J., Postle, A.D., & Rolles, C.J. (1994) Plasma lipid concentrations in children with cystic fibrosis: the value of a high-fat diet and pancreatic supplementation. Brit J Nutr 71:959-64.

Corey, M., McLaughlin, F.J., Williams, M., & Levison, H. (1988) A comparison of survival, growth, and pulmonary function in patients with cystic fibrosis in Boston and Toronto. J Clin Epidemiol 41: 583-91.

Cox, D., & D. Oakes (1984) Analysis of survival data. (Chapman and Hall, London).

Cystic Fibrosis Foundation (1994) Microbiology and infectious disease in cystic fibrosis. (Cystic Fibrosis Foundation, Bethesda).

Cystic Fibrosis Foundation (2002) Cystic Fibrosis Foundation patient registry annual data report. (Cystic Fibrosis Foundation, Bethesda).

Dalzell, A.M., Shepherd, R.W., Cleghorn, G.J., Holt, T.L., & Francis, P.J. (1992) Nutritional rehabilitation in cystic fibrosis: A 5 year follow-up study. J Pediatr Gastroenterol Nutr 15: 141-5.

Dodge. J.A. (1988) Nutritional requirements in cystic fibrosis: A review. J Pediatr Gastroenterol Nutr 7: S8-11.

Driskell, R.A., & J.F. Engelhardt (2003) Current status of gene therapy for inherited lung diseases. Annu Rev Physiol 65: 585-12.

Elborn, J.S., Shale, D.J., & Britton, J.R. (1991) Cystic fibrosis: Current survival and population estimates to the year 2000. Thorax 46: 881-5.

Feranchak, A.P., Sontag, M.K., Wagener, J.S., Hammond, K.B., Accurso, F.J., & Sokol, R.J. (1999) Prospective, long-term study of fat-soluble vitamin status in children with cystic fibrosis identified by newborn screen. J Pediatr 135: 601-10.

Ferrari, S., Griesenbach, U., Geddes, D., & Alton, E. (2003) Immunological hurdles to lung gene therapy. Clin Exp Immunol 132: 1-8.

FitzSimmons, S.C. (1993) The changing epidemiology of cystic fibrosis. J Pediatr 122: 1-9.

Francisco, M.P., Wagner, M.H., Sherman, J.M., Theriaque, D., Bowser, E., & Novak, D.A. (2002) Ranitidine and omeprazole as adjuvant therapy to pancrealipase to improve fat absorption in patients with cystic fibrosis. J Pediatr Gastroenterol Nutr 35: 79-83.

Gaskin, K.J. (1988) The impact of nutrition in cystic fibrosis: A review. 7: S12-7.

Hatta, S., Sakamoto, J., & Horio, Y. (2002) Ion channels and diseases. Med Electron Microsc 35: 117-26.

Hendeles, L., Dorf, A., Stecenko, A., & Weinberger, M. (1990) Treatment failure after substitution of generic pancrealipase capsules. JAMA 263: 2459-61.

Hodson, M.E., & D.M. Geddes (2nd Edition) (2000) Cystic fibrosis. (Arnold, London).

Hopkin, K. (1998) Understanding cystic fibrosis. (University Press of Mississippi, Jackson).

Ionescu, A.A., Nixon, L.S., Luzio, S., Lewis-Jenkins, V., Evans, W.D., Stone, M.D., Owens, D.R., Routledge, P.A., & Shale, D.J. (2002) Pulmonary function, body composition, and protein catabolism in adults with cystic fibrosis. Am J Respir Crit Care Med 165: 495-500.

Johannesson, M., Gottlieb, C., & Hjelte, L. (1997) Delayed puberty in girls with cystic fibrosis despite good clinical status. Pediatrics 99: 29-34.

Kalivianakis, M., Minich, D.M., Bijleveld, C.M., van Aalderen, W.M., Stellaard, F., Laseur, M., Vonk, R.J., & Verkade, H.J. (1999) Fat malabsorption in cystic fibrosis patients receiving enzymes replacement therapy is due to impaired intestinal uptake of long-chain fatty acids. Am J Clin Nutr 69: 127-34.

Karlberg, J., Kjellmer, I., & Kristiansson, B. (1991) Linear growth in children with cystic fibrosis. Acta Paediatr Scand 80: 508-14.

Kennedy, M.J. (2001) Inflammation and cystic fibrosis pulmonary disease. Pharmacotherapy 21: 593-03.

Kerem, E., Reisman, J., Corey, M., Canny, G., & Levison, H (1992) Prediction of mortality in patients with cystic fibrosis. N Engl J Med 326: 1187-91.

Kulczycki, L.L., Kostuch, M., & Bellanti, J.A. (2003) A clinical perspective of cystic fibrosis and new genetic findings: Relationship of CFTR mutations to genotype-phenotype manifestations. Am J Med Genet 116A: 262-7.

Lanksich, P.G., & E.P. DiMagno (1999) Pancreatic disease: State of the art and future aspects of research. (Springer, Berlin).

Lees, C.M., & R.L.Smyth (2000) The current management of cystic fibrosis. IJCP 54: 171-9.

Levine, J. (1998) Nuritional supplementation in cystic fibrosis: Are all patients candidates for aggressive therapy? J Pediatr Gastroenterol Nutr 27: 120-1.

Marin, O.E., Glassman, M.S., Schoen, B.T., & Caplan, D.B. (1994) Safety and efficacy of percutaneous endoscopic gastrostomy in children. AJG 89: 357-61.

Miller, M., Ward, L., Thomas, B.J., Cooksley, W.G., & Shepherd, R.W. (1982) Altered body composition and muscle protein degradation in nutritionally growth-retarded children with cystic fibrosis. Am J Clin Nutr 36: 492-9.

Moore, M.C., Greene, H.L., Donald, W.D., & Dunn, G.D. (1986) Enteral-tube feedings as adjunct therapy in malnourished patients with cystic fibrosis: a clinical study and literature review. Am J Clin Nutr 44: 33-41.

National Cystic Fibrosis Research Foundation (1971) Guide to diagnosis and management of cystic fibrosis. (National Cystic Fibrosis Research Foundation, Atlanta).

Navarro, J., Munch, A., & Varille, V. (1995) Energy balance and nutritional support in cystic fibrosis. Pediatr Pulmonol 11: 74-5.

Neglia, J.P., Wielinski, C.L., & Warwick, W.J. (1991) Cancer risk among patients with cystic fibrosis. J Pediatr 119: 764-6.

NIH Consensus Statement Online (1997) Genetic Testing for Cystic Fibrosis. Apr 14-16 [2003, July, 24]; 15(4): 1-37.

O'Loughlin, E., Forbes, D., Parsons, H., Scott, B., Cooper, D., & Gall, G. (1986) Nutritional rehabilitation of malnourished patients with cystic fibrosis. Am J Clin Nutr 43: 732-7.

Orenstein, D. (1997) Cystic fibrosis: A guide for patient and family. (Lippincott-Raven, Philadelphia).

Pencharz, P.B. (1983) Energy intakes and low-diets in children with cystic fibrosis. J Pediatr Gastroenterol Nutr 2: 400-2.

Ramsey, B.W., Farrell, P.M., Pencharz, P., & the Consensus Committee (1992) Nutritional assessment and management in cystic fibrosis: a consensus report. Am J Clin Nutr 55: 108-16.

Ratjen, F. & G. Doring (2003) Seminar: cystic fibrosis. Lancet 361: 681-9.

Richardson, I., Nyulasi, I., Cameron, K., Ball, M., & Wilson, J. (2000) Nutritional status of an adult cystic fibrosis population . Nutr 16: 255-9.

Rivers, J.P., & A.G. Hassam (1975) Defective essential-fatty acid metabolism in cystic fibrosis. Lancet 2: 642-3.

Rombeau, J.L., & R.H. Rolandelli (1997) Enteral and tube feeding. (W.B. Saunders Company, Philadelphia).

Rosenfeld, M., Pepe, M., Longton, G., Emerson, J., FitzSimmons, S., & Morgan, W. (2001) Effect of choice of reference equation on analysis of pulmonary function in cystic fibrosis patients. Pediatr Pulmonol 31: 227-37.

Rossi, E., & E. Stoll (1968) Modern problems in pediatrics.(S. Karger, Switzerland).

Samour, P.Q., Helm, K.K., & Lang, C.E. (2nd Edition) (1999) Handbook of Pediatric Nutrition. (Aspen Publishers, Inc., Gaithersburg).

SAS/STAT (2001) SAS/STAT Version 8.02 (SAS Institute Inc., Cary, North Carolina).

Schechter, M.S., & P.A. Margolis (1998) Relationship between socioeconomic status and disease severity in cystic fibrosis. J Pediatr 132: 260-4.

Shale, D. (1996) Cystic Fibrosis. (BMJ Publishing Group, London).

Shepherd, R.W., Cooksley, W.G., & Domville Cooke, W.D. (1980) Improved growth and clinical, nutritional, and respiratory changes in response to nutritional therapy in cystic fibrosis. J Pediatr 97: 351-7.

Shepherd, R.W., Holt, T.L., Thomas, B.J., Kay, L., Isles, A., Francis, P.J., & Ward, L.C. (1986) Nutritional rehabilitation in cystic fibrosis: Controlled studies of effects on nutritional growth retardation, body protein turnover, and course of pulmonary disease. J Pediatr 109: 788-94.

Sheppard, D.N. & M.J.Welsh (1999) Structure and function of the CFTR chloride channel. Physiological Reviews 79: S23-45.

Snell, G.I., Bennetts, K., Bartolo, J., Levvey, B., Griffiths, A., Williams, T., & Rabinov, M. (1998) Body mass index as a predictor of survival in adults with cystic fibrosis referred for lung transplantation. J Heart Lung Transplant 17: 1097-103.

Stallings, V.A., Fung, E.B., Hofley, P.M., & Scanlin, T.F. (1994) Acute pulmonary exacerbation is not associated with increased energy expenditure in children with cystic fibrosis. J Pediatr 132: 493-9.

Stapleton, D., Kerr, D., Gurrin, L., Sherriff, J., & Sly, P. (2001) Height and weight fail to detect early signs of malnutrition in children with cystic fibrosis. J Pediatr Gastroenterol Nutr 33: 319-25.

Steinkamp, G. & H. von der Hardt (1994) Improvement of nutritional status and lung function after long-term nocturnal gastrostomy feedings in cystic fibrosis. J Pediatr 124: 244-9.

Vaisman, N., Clarke, R., & Pencharz, P. (1991) Nutritional rehabilitation increases resting energy expenditure without affecting protein turnover in patients with cystic fibrosis. J Pediatr Gastroenterol Nutr 13: 383-9.

Walker, S.A., & D. Gozal (1998) Pulmonary function correlates in the prediction of long-term weight gain in cystic fibrosis patients with gastrostomy tube feedings. J Pediatr Gastroenerol Nutr 27: 53-6.

Welsh, M.J. & A.E. Smith (1995) Cystic fibrosis. Scient Am 273: 52-9.

Williams, S.G., Ashworth, F., McAlweenie, A., Poole, S., Hodson, M.E., & Westaby, D. (1999) Percutaneous endoscopic gastrostomy feeding in patients with cystic fibrosis. Gut 44: 87-90.

Wilson, D.C., Rashid, M., Durie, P., Tsang, A., Kalnins, D., Andrew, M., Corey, M. Shin, J., Tullis, E., & Pencharz, P.B. (2001) Treatment of vitamin K deficiency in cystic fibrosis: Effectiveness of a daily fat-soluble vitamin combination. J Pediatr 138: 851-5.

Zemel, B.S., Jawad, A.F., FitzSimmons, S., & Stallings, V.A. (2000) Longitudinal relationship among growth, nutritional status, and pulmonary function in children it cystic fibrosis: Analysis of the cystic fibrosis foundation national CF patient registry. J Pediatr 137: 374-80.

Zielenski, J., Rozmahel, R., Bozon, D., Kerem, B., Grzelczak, Z., Riordan, J., Rommens, J., & Tsui, L. (1991) Genomic DNA sequence of the cystic fibrosis transmembrane conductance regulator (CFTR) gene. Genomics 10: 214-28.

BIOGRAPHICAL SKETCH

Elizabeth Beasley was born in Roanoke, Virginia, and raised in Boone, North Carolina and Statesboro, Georgia. She attended Statesboro High School, where she graduated with honors in 1998. In 2001, she graduated cum laude from the University of Georgia (UGA), Athens, Georgia, with a Bachelor of Science in family and consumer sciences majoring in dietetics. While at the University of Georgia, she was inducted into the Honor Society of Phi Kappa Phi, served as the UGA chapter president of Phi Sigma Pi National Honor Fraternity, and was named the College of Family and Consumer Sciences Outstanding Senior.

In 2003 she obtained her Master of Science degree from the University of Florida in the Food Science and Human Nutrition Department and was named the Outstanding Dietetics Student for the state of Florida by the Florida Dietetic Association. She plans to pursue a career in pediatric nutrition with the goal of providing excellent nutrition care to children with malnutrition and nutrition-related disorders.