Pulm.

Medical Grand Rounds

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CYSTIC FIBROSIS IN ADULTS

K. Joy Robertson, M.D.
University of Texas Health Science Center at Dallas

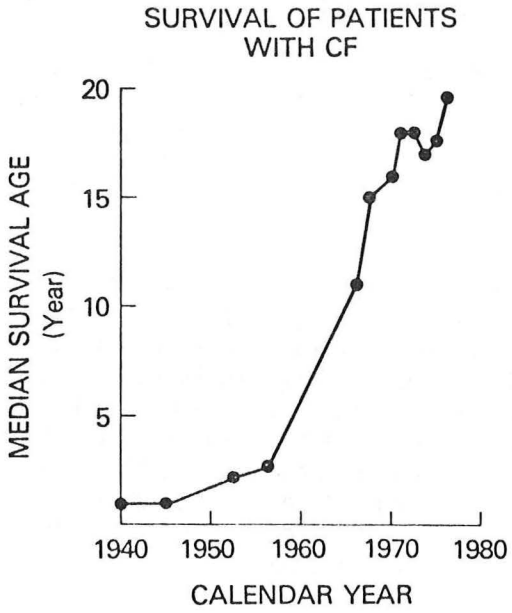
I. Introduction

> Das Kind stirbt bald Wieder, dessen Stirne
> beim Küssen salsig schmekt (1).

"The child will soon die, whose brow tastes salty when kissed", a quotation from Medieval German folklore, is the earliest known reference to the condition now known as cystic fibrosis (1). Subsequent early reports described many of the clinical manifestations, meconium ileus, and the pathologic changes in the pancreas (2-5). In 1936 Fanconi first related congenital cystic pancreatic fibrosis to bronchiectasis (6). However, it was not until 1938 that Anderson described the syndrome as a distinct clinical entity using the term cystic fibrosis (CF) of the pancreas (7). In the 1940's it was recognized that many of the clinicopathologic changes could be explained by a generalized defect in mucous secretions and the term "mucoviscidosis" was coined. In 1953, di Sant'Agnese corroborted this observation by demonstrating abnormal sweat electrolytes and generalized exocrine gland dysfunction in patients with CF (8).

Cystic fibrosis is the most frequent lethal genetic disease of white Americans. Despite intensive investigation in the 48 years since it was first described the underlying biochemical error remains unknown. Nevertheless, the clinical manifestations of the syndrome are well described.

Figure 1



The dramatic improvement in median survival in this disorder from less than 2 years in 1940 to greater than 25 years today is presented in Figure 1 (9). It is estimated that there are greater than 30,000 patients with CF in the United States, about 20 percent of whom are adults, and these numbers are steadily increasing (10). Approximately 20 percent of cases are now diagnosed after 15 years of age (11). The improved survival of cases diagnosed in childhood and the diagnosis of adult cases dictate that cystic fibrosis can no longer be ignored by internists.

Although cystic fibrosis is a multisystem disease, this report will emphasize the pulmonary manifestations as well as diagnostic criteria and management, and certain immunologic abnormalities present in adult patients. Gastrointestinal, genitourinary and exocrine gland function will be addressed only in regard to diagnosis and prognosis.

II. Genetics

Cystic fibrosis occurs in Caucasian, Black and Mongoloid races with the incidences listed in Table 1 (9).

Table 1

Incidence of Cystic Fibrosis

Race	Live Births
Caucasian	1: 2,000
Black	1:17,000
Mongoloid	1:90,000

Most studies of the genetics of CF support an autosomal recessive inheritance pattern (12-14). There is therefore a 1:4 chance of each pregnancy producing a CF child when both parents are carriers of the gene. Approximately 4-5 percent of the Caucasian population have the abnormal CF gene; these persons have no identifying clinical characteristics (15). Cystic fibrosis is not linked genetically with ABH blood groups (16), MNS blood groups (17) or HLA antigens (18). CF has been diagnosed in patients with one of several other genetic diseases, but a causal linkage with these diseases has not been apparent (19).

There is no suitable method to screen for carrier detection in cystic fibrosis (20). However, prospective prenatal diagnosis by aminocentesis is promising (21, 22).

Since the biochemical defect has not been identified, effort has been expended to define the responsible genetic locus (23). Recent reports have identified the CF locus on chromosome 7 probably between bands q21 and q31 (24-27). This area of investigation will no doubt come to fruition in the near future and thus allow appropriate genetic counseling.

III. Clinical Definition

Although an autosomal recessive inheritance for cystic fibrosis suggests a discrete biochemical or structural defect to account for the pathophysiologic manifestations, none has been identified. Thus, the definition continues to depend on clinical findings, and cystic fibrosis remains a syndrome. The four criteria given in Table 2 are generally utilized in making the diagnosis (28).

Table 2

Diagnostic Criteria for Cystic Fibrosis

Sweat Chloride >60 meq/l
Chronic obstructive pulmonary disease
Exocrine pancreatic insufficiency
Family history

The sweat chloride test has been widely accepted as the *sine qua non* for diagnosis, and its use in adults will be presented in detail later in the discussion. In adults, as in children, the combination of chronic obstructive pulmonary disease and intestinal malabsorption are characteristics of almost all patients. However, with increasing age symptoms due to pancreatic insufficiency diminish, while those due to chronic obstructive pulmonary disease dominate. A family history of CF is not always present, but it is very helpful if confirmed cases are known. Most authorities require an elevated sweat chloride and at least one of the other criteria for a diagnosis.

IV. Age at Diagnosis

Table 3 presents the spectrum of age at diagnosis for 145 adult patients (29, 30).

Table 3

Age at Diagnosis for 145 Patients
Over the Age of 18

Years	Number of Patients	Percent
0-5	69	48
6-15	43	30
15-20	20	14
21-25	8	6
>25	5	3

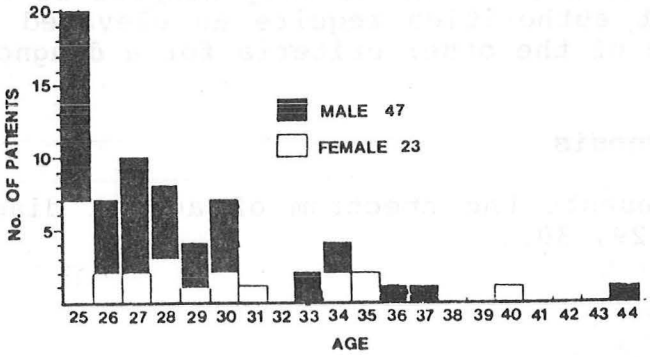
From this unselected population it can be seen that approximately 80 percent of patients are appropriately diagnosed before the age of 15 years. However, over 20 percent may not be recognized until adolescence or later. Among these patients, a majority will have long standing typical symptoms but only minimal to moderate debility and thereby escape appropriate diagnosis. There are increasing reports, however, of small numbers of patients whose initial symptoms do not occur until adolescence or later and of adults who are virtually asymptomatic (31). These patients challenge the acumen of the internist.

V. Sex

The sex distribution of older patients is significantly different from that observed in childhood. Figure 2 presents the age and sex distribution of 70 patients over the age of 25 years (30).

Figure 2

Age and Sex Distribution of 70 Patients
With CF Over 25 Years of Age



This and other studies indicate a marked male predominance in older patients. Indeed, approximately 70 percent of newly diagnosed cases over the age of 15 years are men (31). In contrast, during infancy and childhood 48 percent of patients are girls and 52 percent are boys (29, 32). The childhood ratio is in keeping with an autosomal recessive inheritance. The changing sex ratio with advancing age supports the premise that girls with cystic fibrosis die at an earlier age than boys.

VI. Respiratory-Pathology

Although lung disease in cystic fibrosis is characterized clinically and pathologically by variability in onset and evolution, the changes listed in Table 4 are well described in most autopsy series (33).

Table 4

Lower Respiratory Pathology in
Cystic Fibrosis

Normal at birth
Bronchial gland hypertrophy
and hyperplasia
Mucous plugging
Infection
Peripheral airway dilatation
Bronchial artery hypertrophy

Infants dying of meconium ileus have been found to have morphologically normal lungs. Therefore, it is assumed that the immunologic, biochemical or structural defect responsible for the lung damage is expressed post natally. The earliest lesions are dilation and hypertrophy of bronchial glands and goblet cells in association with squamous metaplasia of the bronchiolar epithelium; mucous plugging and dilation of peripheral airways then supervenes (34-36). Infection follows, and a cycle of obstruction, chronic infection and atelectasis results in peribronchial fibrosis, bronchiectasis and cyst formation, usually without destruction of alveolar septa (37, 38). In severe cases bronchiectasis results in bronchial artery hypertrophy and shunting of blood from the bronchial arteries to the pulmonary circulation (38, 39). In a recent autopsy series of 17 young adults dying with CF, these changes were quantitatively shown to occur more severely in the upper lobes (40). The study emphasizes the uneven nature of the lung remodeling.

VII. Clinical Disease in Adults

Until the advent of antibiotics the early mortality of CF patients prevented an appreciation of the variability in the clinical presentation and severity of disease. It is now apparent, however, that the features are quite different among patients, and this heterogeneity frequently obscures the diagnosis. The signs and symptoms of cystic fibrosis in the adult can be considered under the headings of pulmonary, gastrointestinal, growth and development, genitourinary and sweat gland.

Pulmonary

As previously indicated, pulmonary symptoms predominate in the adult. The symptoms listed in Table 5 are a compilation of five series comprising 247 adolescent and adult patients (29, 41).

Table 5

Respiratory Symptoms of Cystic Fibrosis in 247 Adult Patients

Symptom	Percent
Cough	97
Sputum production	90
Rhinitis ± sinusitis	84
Hemoptysis	60
Wheezing	58
Dyspnea (mild)	47
Dyspnea (severe)	5
Chest pain	1

Chronic cough and sputum production occur almost universally, even when the patient is not clinically infected. Symptoms of rhinitis and sinusitis are almost as common as sputum production, and symptoms of nasal obstruction occur at some time in 75 percent of patients. Minor hemoptysis is present in greater than 60 percent of patients and is not related to worsening of disease (41). Intermittent hemoptysis is more common in cystic fibrosis than in bronchiectasis; however, it is massive in less than 7 percent of CF patients (28). The intermittent wheezing which occurs in over 50 percent of CF patients is another feature which distinguishes them from patients with bronchiectasis. Dyspnea is present in half of

patients but is described as moderate until late in course of the disease. Pleuritic chest pain is rare even in the presence of pneumothorax (41).

Significant respiratory physical findings are listed in Table 6.

Table 6

Respiratory Signs in 71 Adult Patients with Cystic Fibrosis

Sign	Percent
Finger clubbing	73
Wheezes-intermittent	58
Nasal polyps	50
Rales	42
Chest deformity	26

Finger clubbing occurs in a majority of adult patients without correlation to clinical grading or severity of disease. Intermittent wheezing and nasal polyposis may occur concomitently or as separate findings in over half of patients. Rales and rhonchi are present in less than 50 percent of adults and have been described as an early sign of pulmonary disease (42, 43). In contrast to children, adults are much less likely to have a pigeon breast or other chest wall deformity, and most are reported to have normal rib cage movement (42).

Gastrointestinal

Gastrointestinal signs and symptoms are listed in Table 7.

Table 7

Gastrointestinal Signs and Symptoms in 258 Adult Patients with Cystic Fibrosis

Sign or Symptom	Percent
Pancreatic insufficiency	95
Abdominal distention	30
Intestinal obstruction	15
Hepatosplenomegaly	10
Cirrhosis	5

Pancreatic insufficiency and maldigestion manifest by greater than 2 bowel movements per day and increased fecal fat excretion occur as commonly as pulmonary symptoms; however, these complaints are much milder in adults than in children. The need for pancreatic replacement and dietary restriction may actually decrease with advancing age (29, 42, 44). There is no evidence of other associated maladsorption syndromes such as coeliac disease or diasaccharide intolerance, both of which have been described in childhood (45-47). Complaints of abdominal distension occur in one-third of patients, but frank intestinal obstruction with either mucoidinspissation, or meconium-ilius equivalent presenting with intussusception is found in less than 15 percent of adults (29, 42, 47). Hepatosplenomegaly is present in a minority of patients. Although signs and symptoms of hepatic cirrhosis are occasionally the presenting symptom in otherwise asymptomatic adults, the overall occurrence is only 5 percent (31, 42).

Growth and Development

Patients who present in infancy or early childhood with severe pulmonary and gastrointestinal symptoms manifest retarded growth and development with a small body habitus and the changes of a chronic debilitating disease. In contrast, Table 8 summarizes the characteristics of 41 adolescent and adult patients (31, 41).

Table 8

Growth and Development in 41 Patients with CF Diagnosed After the Age of 15

Parameter	Number	Percent
Height <30th percentile	4	10
Weight <30th percentile	23	56
Delayed puberty	5	12

Patients who are diagnosed after the age of 15 are generally of normal height with only 10 percent below the 30th percentile. In one series a majority of the patients 18 years and older were above the 90th percentile in height (29). Although older patients are normal to tall, at least half are of subnormal weight. However, nutritional scores are good even in most of those in the low weight group. Puberty and growth acceleration may be delayed in a minority of adolescents, and this finding seems to correlate with severe disease.

Genitourinary and Sweat Gland

Other clinical signs and symptoms which aid in the recognition of cystic fibrosis in the adult are listed in Table 9.

Table 9

Other Clinical Features of
Cystic Fibrosis in Adults

Sign or Symptom	Percent
Sterility	
Men	97
Women	70-85
Sweat Gland	
Excessive sweating	60-95
Heat prostration	6

Sterility in men with cystic fibrosis was described in 1968 (48-51). There is bilateral absence or atrophy of the epididymis, vas deferens and seminal vesicles, decreased semen volume and aspermia (34, 48, 51). These changes result in an infertility rate of 95-97 percent. Nevertheless, sexual function is preserved, and there are occasional reports of men with normal semen analysis who have fathered children (48, 52).

In contrast to men, women display no major anatomic reproductive abnormality (34). The actual incidence is unknown, but infertility has been reported to be between 70 and 85 percent (29, 30, 53). Decreased water content of cervical mucus is believed responsible for this reproductive failure (54-56). Complications are common in pregnant women with cystic fibrosis and are correlated with the severity of pulmonary dysfunction. Among 70 pregnancies with a known outcome, 46 viable infants were produced (13). The risk of a homozygous mother and a father of unknown genetic status having a child with CF is 1 in 40 (57).

Although all patients with cystic fibrosis have abnormal electrolyte concentrations in sweat, clinical symptomatology of excessive sweating is variably described. Common complaints include salty taste, excessive staining of clothing, frosting of skin, and rusting of metal handled by cystic employees in an industrial setting (28, 58). Massive loss of salt and water via sweat frequently leads to cardiovascular collapse in infants (59), but heat prostration has been reported in only 6 percent of

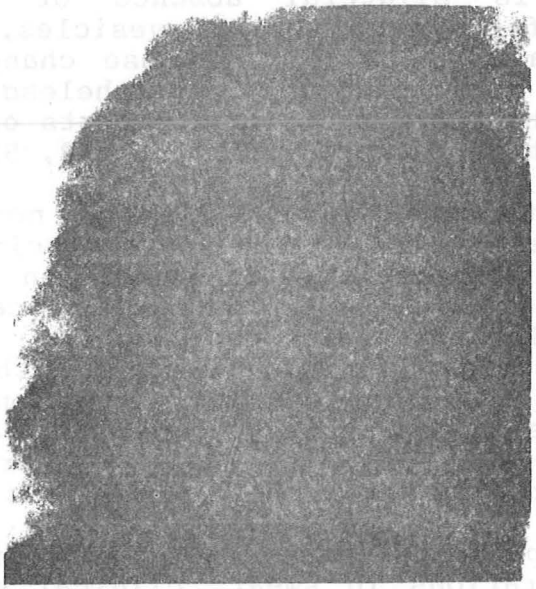
adult patients (29). Chronic salt loss is also the presumed mechanism of a low systolic and diastolic blood pressures in adults with cystic fibrosis (59).

VIII. Radiology

Radiographic changes in cystic fibrosis are sufficiently distinct to suspect the diagnosis. There is excellent radiographic correlation with pathologic findings; infiltrates and cystic remodeling of the lung occur predominately in the upper lobes, especially the right upper lobe (40). Early radiographic changes in the RUL of an adult patient with CF are presented in Figure 3.

Figure 3

Early Radiographic Changes
in Cystic Fibrosis in the Right Upper Lobe

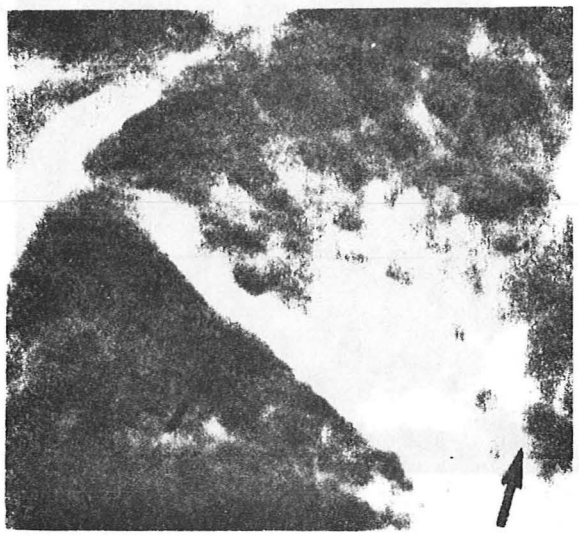


There is general haziness of the vascular markings which are irregular, discontinuous and have a reticulonodular appearance. The nodular and linear densities are small and peripheral but spare the outer centimeter of lung. The evolution of these small densities indicate that they represent focal inflammatory infiltrates centered on the airways (60). These shadows rarely regress and are subsequently associated with upward hilar

retraction. Typical progression of the RUL disease is presented in Figure 4.

Figure 4

Late Radiographic Changes
of Cystic Fibrosis in the Right Upper Lobe

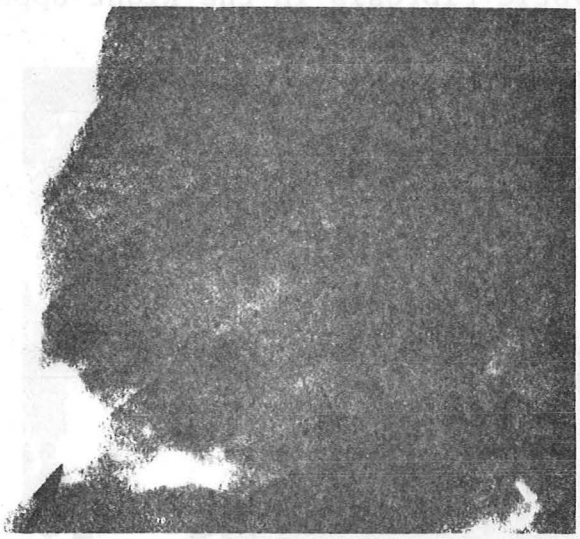


There is enlargement of peripheral densities which become cystic or ring-like with central lucencies. In Figure 4 these lucencies are best appreciated below the horizontal fissure. The cystic areas represent ectatic bronchi and bronchioles which are seen on end. As the bronchial wall thicken and interstitial infiltration progresses, a typical honeycomb appearance ensues as demonstrated above the fissure in Figure 4. The lower arrow points to a typically thick walled, dilated and distended bronchus which is seen in profile producing a cyst. Some authors have described this advanced stage as a bizarre, distorted picture suggestive of swiss cheese (61).

A third fairly typical radiographic pattern is shown in Figure 5.

Figure 5

Transient Nodular Densities
in Cystic Fibrosis in the Right Upper Lobe



Transient nodular densities have been described in up to 40 percent of patients at some time during their illness. These densities occur among air containing, dilated bronchi and cannot be appreciated in late stages of disease (61). Correlative pathology studies indicate that these evanescent nodularities consist of endobronchial abscesses that drain by rupture into adjacent bronchi (62).

Hyperinflation, cystic bronchiectasis and lobar atelectasis are also characteristic radiographic changes in adult patients; their relative incidences are tabulated in Table 10.

Table 10

Chest Roentgenographic Findings
in 283 Adult Patients with Cystic Fibrosis

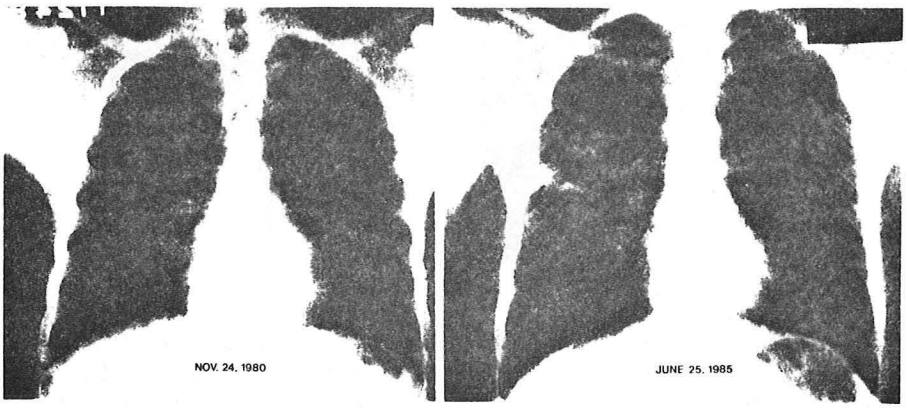
Ref.	Pt. (no.)	Interstitial Markings (no.)	Bronchiectasis (no.)	Large Lung Volumes (no.)	Atelectasis (no.)
29	75	71	59	36	12
30	70	70	24	64	11
61	55	55	44	28	1
60	50	45	45	38	20
53	33	30	25	28	5
	283	271 (96%)	197 (70%)	194 (68%)	49 (18%)

In this large number of patients, 96 percent had an increase in perivascular or peribronchial markings causing an interstitial appearance. This finding is usually bilateral with a perponderance in the upper lobes particularly on the right. With increasing severity of disease upper lobe cystic bronchiectasis is found in 70 percent. Since the basic respiratory tract lesion leading to bronchiectasis is obstruction of airways, three-fourths of patients have hyperinflated lung volumes despite the presence of interstitial parenchymal disease. This finding is in contrast to the radiographs of infants with CF which may appear emphysematous but lack parenchymal lung infiltrates (63). Lobar atelectasis and mucus plugging occur in 20 percent of patients and are more severe lesions. When atelectasis develops it is almost always upper lobe, does not respond to treatment, and is almost never transient (60, 61).

Radiographic changes of early disease are presented in Figure 6.

Figure 6

Chest Radiography of Early
Progressive Cystic Fibrosis in an Adult



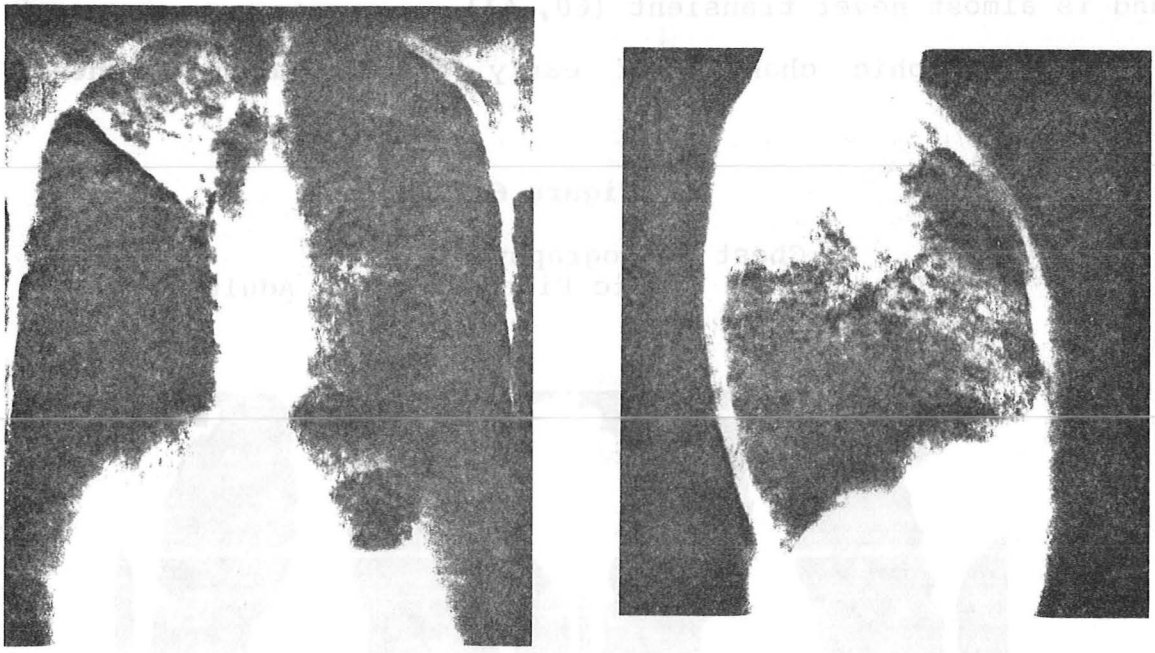
Initial radiographs are non-specific; they may be interpreted as normal or bilaterally increased, non-specific markings compatible with an interpretation of "dirty" lungs, a finding often associated with asthma or chronic bronchitis. In this patient the radiograph progressed over a 5 year period into typical bilateral infiltrates with right upper lobe nodular disease sparing the periphery. The lung volumes are increased, and interstitial markings spare the bases. These findings differ

from most chronic interstitial lung diseases which have a propensity for the bases and result in small lung volumes.

Figure 7 is representative of all the typical radiographic changes in advanced cystic fibrosis.

Figure 7

Chest Radiographs of Advanced Cystic Fibrosis in the Adult



These radiographs are those of a young person as estimated by bone age. There is extensive, bilateral, parenchymal interstitial lung disease that is less marked in the bases and lung periphery. Additionally, the lung volumes are large, and there is severe right upper lobe cystic disease with atelectasis and bronchial dilation.

Additional radiographic changes may be found late in the course of CF. The incidence of these changes in one series are listed in Table 11.

Table 11

Radiographic Pulmonary Complications in 55 Adults with Cystic Fibrosis

Complication	Percent
Right heart and pulmonary vascular enlargement	47
Hilar retraction	30
Pneumonia	30
Pneumothorax	10

Mortality from cystic fibrosis is almost exclusively due to the lung changes which may lead to cor pulmonale with right heart enlargement as a preterminal event. The radiographic changes of pulmonary hypertension are indistinguishable from those of other lung diseases resulting in right heart failure. Upward hilar retraction occurs with severe cystic changes, often in association with apical bullae. Pneumonia is difficult to identify due to the patchy infiltrative nature of the underlying disease. The diagnosis is usually based on finding small peribronchial infiltrates in the presence of a compatible clinical presentation that resolve with antimicrobial therapy. Lobar consolidation is distinctly rare and occurred in only 3 of 55 patients in this series. Pneumothorax occurred in 10 percent of patients in this series; this event will be discussed subsequently (61).

IX. Differential Diagnosis

An incorrect assessment of the presenting signs, symptoms and chest radiographs, and a low index of suspicion of cystic fibrosis in adults, frequently results in an inappropriate diagnosis. The diagnoses among 54 adult patients are listed in Table 12 (30, 31).

Table 12

Incorrect Diagnoses Among 54 Adult Patients with Cystic Fibrosis

Diagnosis	Number	Mean Length of Treatment (yrs.)
Celiac Disease	19	4.5
Asthma	8	4.0
Bronchiectasis	6	7.5
Bronchitis	5	NS*
Tuberculosis	4	1
Sarcoidosis	2	NS*
Histoplasmosis	1	1.5
Cirrhosis	1	NS*
Miscellaneous	2	NS*
Normal	6	--

*NS=not stated

The most common misdiagnosis was celiac disease. The mean duration of treatment with a gluten free diet was 4.5 years with a range of 3 to 15 years. Patients with either CF or celiac disease may present with diarrhea and abdominal distention. However, pulmonary symptoms, infertility and sweating abnormalities are not reported in adult celiac disease, and 90 percent of patients respond to a gluten free diet within 1-2 weeks. Intermittent wheezing occurs in cystic fibrosis in the absence of asthma, and the two conditions both exist in some patients (64). Abnormalities of chest radiographs, clubbing or rales suggest another diagnosis than simple asthma. Pathologic changes of bronchiectasis and bronchitis both occur in patients with cystic fibrosis. A history of gastrointestinal symptoms, sterility or sweating abnormalities should suggest further investigation of patients with these conditions. Reactivation tuberculosis and histoplasmosis present with symptoms of a chronic infectious disease, and chest radiographs do not show hyperinflation or the changes of cystic bronchiectasis. Sarcoidosis is common in black persons in whom CF is rare. The diffuse interstitial and alveolar infiltrates of sarcoidosis are usually uniform in upper and lower lung fields, and lung volumes are decreased. Patients with CF who present with cirrhosis may be free of lower respiratory symptoms. However, in a study of 25 patients, pansinusitis was present in all patients diagnosed over age 13 (31). Six patients with few or no symptoms were considered normal until the illness was suggested by the diagnosis of a family member.

A history of certain surgical procedures may also suggest cystic fibrosis. Table 13 lists these procedures (30).

Table 13

Surgical Procedures in 32 Adult Patients with Undiagnosed Cystic Fibrosis

Surgical Procedure	Percent
Nasal polypectomy	72
Laparotomy ± appendectomy	35
Bronchoscopy	25
Inguinal hernia, orchidopexy	17
Lobectomy	3

Nasal polypectomy was performed a total of 74 times in 70 patients. One patient had 20 procedures, another 18 and a third 16 (30). Signs and symptoms of multiple recurrent nasal polyposis, even in the presence of allergy, have a high correlation with the diagnosis of CF (65). The gastrointestinal manifestations of undiagnosed CF result in approximately 35 percent of patients having laparotomies, usually without a resultant diagnosis. Bronchoscopy is most commonly performed because of radiographic changes; the procedure never establishes a diagnosis of either CF or bronchiectasis. There is an increased incidence of inguinal hernia, hydrocele and undescended testicles in men with cystic fibrosis; corrective surgery for these conditions in the setting of any other sign or symptom should prompt further investigation (66).

X. Laboratory Abnormalities

Sweat Electrolytes

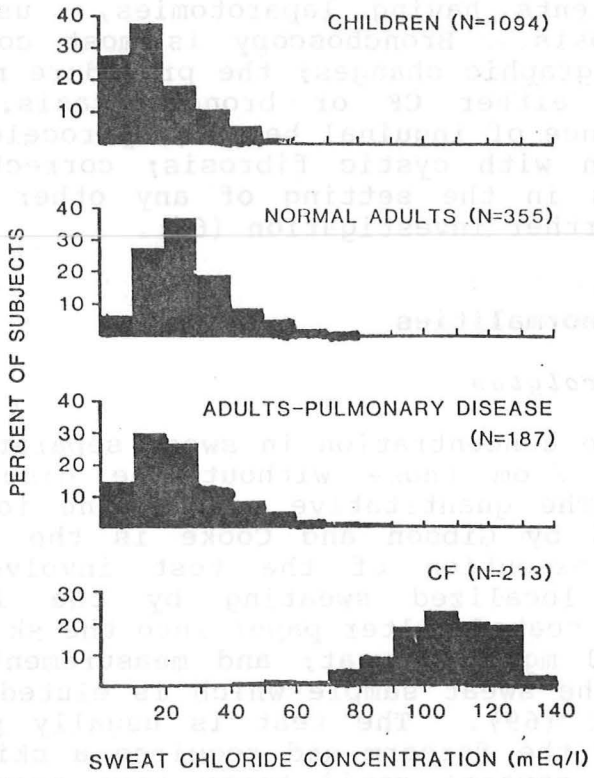
The chloride concentration in sweat separates patients with cystic fibrosis from those without the disease with little overlap (67). The quantitative pilocarpine iontophoresis test (QPIT) described by Gibson and Cooke is the preferred method (68). Proper execution of the test involves three steps: stimulation of localized sweating by the iontophoresis of pilocarpine from soaked filter paper into the skin; collection of greater than 100 mgm of sweat; and measurement of electrolyte composition of the sweat sample which is eluted with water from the filter paper (69). The test is usually performed on the volar surface of the forearm and requires a skilled technician. In recent years several rapid tests have been designed which eliminate tediously weighing the quantity of sweat. An evaluation of these procedures by a multicenter research group organized by the National Cystic Fibrosis Foundation found unacceptable individual variability and recommend they be used

only as screening devices with confirmation of positive results by QPIT (70).

The discriminatory value of the sweat chloride was questioned in adults after recognition that electrolyte concentrations are higher in normal adults than in children (71-75). Recent studies employing the method of Gibson have not only validated the test in adults but also confirmed its value in children and adults in discriminating CF from other pulmonary diseases. The results of sweat chloride determinations performed on 1,849 subjects are depicted in Figure 8 (76).

Figure 8

Sweat Chloride Determination in the Diagnosis of Cystic Fibrosis



The chloride concentration in the sweat of normal children was never over 60 meq/l and separated them from cystics without overlap. Over 98 percent of the patients with cystic fibrosis have a sweat chloride concentration greater than 60 meq/l; 1 to 2 percent have values between 50 and 60 meq/l, and about 1 in 1,000

have values less than 50 meq/l (29, 77). In both normal adults and those with other types of pulmonary disease 99 percent have a sweat chloride <60 meq/l. The most frequent false positive was found in a subgroup of patients with pulmonary disease who also had pancreatitis. Elevated sweat electrolytes have been reported in one-third of patients with pancreatitis (78). "False negative" results may occur in the setting of clinical edema (79, 80).

The most common cause of a false positive test is laboratory error. Table 14 lists some of the clinically distinguishable conditions that have been reported to have elevated sweat chloride concentrations (81-85).

Table 14

Conditions Associated With An Elevated Concentration of Sweat Chloride

Adrenal insufficiency
Ectodermal dysplasia
Nephrogenic diabetes insipidus
Hypothyroidism
Fucodosis

The sweat test is an excellent diagnostic test in adults with cystic fibrosis, and its discriminatory ability has been validated.

Pancreatic Deficiency

Pancreatic dysfunction may be documented by duodenal intubation and measurement of the bicarbonate and enzyme content of duodenal fluid after stimulation of secretion by pancreozymin. Even patients with intact enzyme release have markedly decreased water and bicarbonate secretion (86). This test has little value in clinical practice. Evidence of elevated fecal fat excretion is sufficient to consider enzyme replacement therapy. Other tests for pancreatic dysfunction such as the Boehringer-Mannheim test and assays for blood and stool trypsin levels have unacceptable false negative and false positive rates and have no role in the diagnosis of CF in adults (87).

Routine Laboratory

Routine laboratory examination is not useful in evaluation of adult patients with cystic fibrosis. Hemoglobin has been

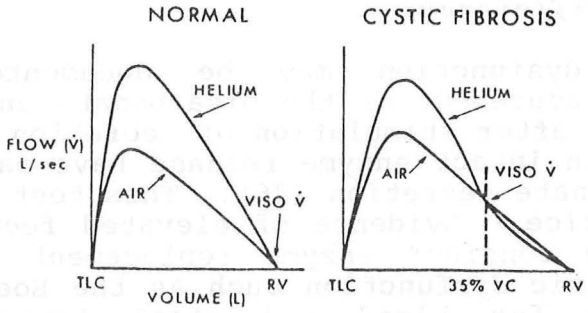
reported to be normal (>13 gms) in 85 percent of patients (29, 41, 42). Polycythemia occurs with advanced pulmonary disease and mild anemia with increasing debilitation. The white blood count is elevated only with clinical infection (42). Parameters of liver function have not been consistently reported; in two series approximately 50 percent of patients had a persistently elevated alkaline phosphatase with levels reported in excess of 140 King-Armstrong units (41, 42).

Pulmonary Function Tests

There is good physiologic correlation with the pathologic observation that the earliest changes in cystic fibrosis are in peripheral airways. Tests of small airway abnormalities such as frequency dependence of compliance, flow rates at low lung volumes, and flow-volume response to helium reveal early abnormalities not demonstrated by standard ventilatory measurements (88-90). Figure 9 demonstrates the schematic representation of a maximal expiratory flow-volume curve breathing room air and following inhalation of a helium-oxygen mixture of a normal child and a child with cystic fibrosis (91).

Figure 9

Flow-Volume Curves After Helium-Oxygen Mixture in Normal Child and a Child with Cystic Fibrosis



In large airways gas flow is turbulent, and the resistance to flow is partially dependent on gas density. In the peripheral airways flow is laminar and independent of gas density. Thus, large but not small airway flow is improved by breathing helium and oxygen which is less dense than nitrogen and oxygen. The curve of a normal child shows that breathing a low density gas mixture causes a marked increase in maximal expiratory flow rates, and the volume of identical flow with both gas mixtures is

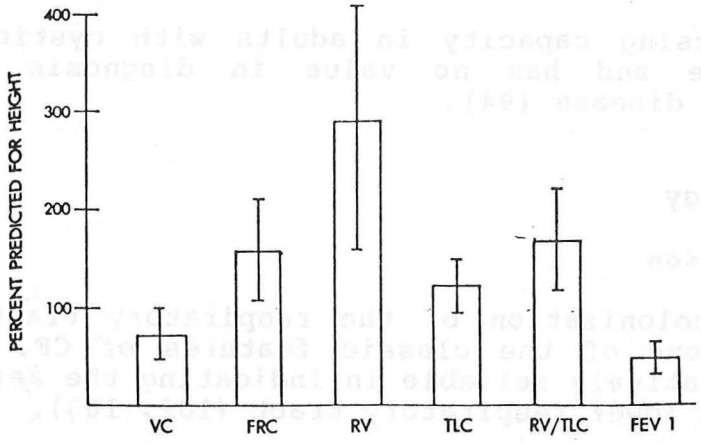
very near residual volume. Thus, the small peripheral airways add little to total resistance. The curve from the child with cystic fibrosis shows that the maximal expiratory flow after breathing the Heli-ox mixture is not improved, and the volume of identical flow breathing both gases is at 35 percent of vital capacity. These findings indicate that the peripheral airways contribute a substantial portion to overall airway resistance.

As the lung disease progresses changes in pulmonary function demonstrate decreases in maximal mid-expiratory flow and forced expiratory volume in 1 second. Loss of elastic recoil of the lung and subsequent air trapping result in elevation of residual volume (RV) and functional residual capacity (FRC) (91). Thoracic gas volume at total lung capacity (TLC) is usually normal or elevated even though the vital capacity may be markedly decreased (92, 93).

Pulmonary function data in adult patients is extremely variable and relate to the clinical severity of disease. The pulmonary function tests of 40 patients over 24 years of age who had been followed from 3 to 29 years are given in Figure 10 (94).

Figure 10

Mean Value (± 1 SD) of Pulmonary Function Tests
of Patients with Cystic Fibrosis Over Age 24
n=40



The mean values at the age of 25 are characteristic of moderate to severe obstructive pulmonary disease with increased FRC, RV, and RV/TLC. However, marked variation between

individuals is evidenced by the large standard deviations of mean values. In this and other series stability and even improvement in some adult patients for periods of seven to ten years has been documented (94, 95). The rate of decline of pulmonary function is significantly greater in women than men, and men out number women by a ratio of 2:1 at this age (94, 95).

Up to 50 percent of patients with CF have increased bronchial reactivity demonstrated by methacholine or histamine challenge (96, 97). In a recent report 95 percent of patients followed for a protracted interval had a significant bronchodilator response to beta adrenergic drugs on at least one occasion. Responsiveness was lost when patients were judged to be free of acute exacerbations of disease (98). The investigators conclude that bronchodilator responsiveness occurs in most subjects during episodes of inflammation, edema and secretion retention.

The diffuse, patchy bronchiolitis and mucus plugging of CF lead to regional ventilation/perfusion abnormalities. The resulting hypoxemia is the earliest sign of lung disease and is observed prior to any dectectable abnormality in lung mechanics (99). The severity of hypoxemia is a good indicator of prognosis; it correlates well with pulmonary deterioration and is associated with the onset of cor pulmonale (100).

As in other patchy lung diseases, an elevated arterial pCO_2 does not occur until the disease is far advanced because of increasing minute ventilation to less affected lung segments. An elevated pCO_2 indicates a near-terminal status (101).

The diffusing capacity in adults with cystic fibrosis is quite variable and has no value in diagnosis or assessing progression of disease (94).

XI. Microbiology

Colonization

Chronic colonization of the respiratory tract by specific organisms is one of the classic features of CF. Cultures of sputum are relatively reliable in indicating the aerobic bacteria colonizing the lower respiratory tract (102, 103).

Results of two series that compared aerobic pathogens from transtracheal aspirate (102) and thoracotomy (103) cultures to washed expectorated sputum cultures are given in Table 15.

Table 15

Comparison of Transtracheal Aspirate and Thoracotomy Cultures to Sputum Cultures in Patients with CF

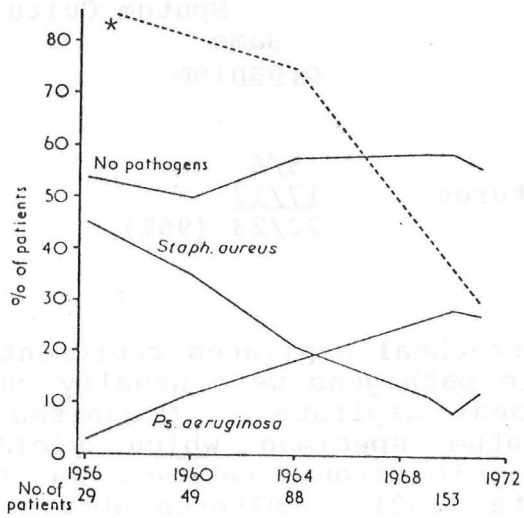
	Sputum Cultures	
	Same organism	Different organism
TTA cultures	5/6	1/6
Thoracotomy cultures	17/17	0/17
	22/23 (96%)	1/23 (4%)

Data from transtracheal aspirates represent 6 procedures in 4 patients. Multiple pathogens were usually cultured from both sputa and transtracheal aspirates. Organisms were comparable except for one sputum specimen which yielded two aerobic pathogens, while a single aerobic pathogen was cultured from the transtracheal aspirate (102). Cultures obtained at thoracotomy included aspirates from the uncut lung specimen and homogenates of the tissue. The aerobic pathogens isolated in this study were identical, and had the same antibiotic sensitivites, in sputa and thoracotomy specimens. Other investigators have obtained similar results (104, 105). It should also be noted that three of 6 TTA cultures and three of 17 thoracotomy specimens yielded anaerobic bacteria which may contribute to ongoing lung destruction.

Soon after the first description of cystic fibrosis it was recognized that the respiratory tract was colonized with bacteria within the first year of life in most patients (106). As early as 1949 Anderson showed that bronchial secretions grew *Staphylococcus aureus* in nearly every case (107). By the late 1950's a change in flora was noted. The results of airway cultures of children under one year of age are compared to those of all other patients attending a cystic fibrosis clinic from 1950 to 1971 in Figure 11.

Figure 11

Bacterial Flora of the Respiratory Tract
of Patients with Cystic Fibrosis
1950-1971



*Staphylococcal colonization of CF infants <1 year old

As indicated by the dashed line, the incidence of colonization of infants under one year of age with *Staphylococcus aureus* decreased from 86 percent in 1956 to 30 percent in 1972. During the same interval the rate of staphylococcal colonization for all other patients attending the clinic dropped from 45 percent to 12 percent. Simultaneously, rates for *Pseudomonas aeruginosa* rose from 3 percent to 28 percent. The percentage of patients with no recognized pathogens remained unchanged at approximately 55 percent. In this study the presence of anti-staphylococcal precipitins had no relation to severity of disease or clinical deterioration with time.

Since 1970 the trend for an increasing fraction of patients to be colonized with pseudomonas has continued. Table 16 is the sum of 3 series of adult patients which indicates the relative rates of colonization by pathogenic bacteria after 1977 (30, 41, 53).

Table 16

Colonization by Pathogenic Bacteria of the Lower Respiratory Tracts of 122 Adult Patients with CF

Organism	Percent
Pseudomonas aeruginosa	70-90
(Mucoid strains)	65
Staphylococcus aureus	20-40
Hemophilus influenzae	33
Pseudomonas cepacia	18
Escherichia coli	13
Aspergillus fumigatus	10
Klebsiella species	7
Miscellaneous pathogens	2-5

Pseudomonas aeruginosa is by far the most common pathogen isolated from patients with CF (108). *P. aeruginosa* can be separated into mucoid and dry strains by colonial morphology. In one laboratory over a fifteen year period mucoid strains were isolated only from CF patients, a finding confirmed in other series (30, 109). Mucoid strains may become nonmucoid on culture media (110), and nonmucoid strains can be induced *in vitro* to produce mucoid coating (111). *In vivo* colonization with mucoid pseudomonas increases with age and is associated with deterioration of pulmonary function and a poor prognosis (94). After a patient becomes colonized antimicrobial therapy never results in elimination of the organism.

Although overall prevalence of colonization with *S. aureus* is decreasing, most investigators find that it is frequently the initial pathogen cultured and is later supplanted by pseudomonas (112). Simultaneous staphylococcal and pseudomonal colonization is not infrequent. Staphylococcal organisms are of differing phage types, and their role, if any, in pulmonary deterioration has not been clearly defined.

With improving cultural techniques *Hemophilus influenzae* has been isolated in up to one-third of adult patients (30). The strains are usually nontypable. In some series the incidence of serum precipitating antibodies against *H. influenzae* has been as high as 80 percent, but the significance of this finding has not been further investigated (113).

Recent attention has focused on the isolation of the pathogen *Pseudomonas cepacia* which is usually resistant to most antibiotics. It has been recovered in up to 18 percent of adult patients (114). Nosocomial infection has been implicated but not substantiated; however, colonization is more frequent in patients intensively treated with antibiotics. Three patterns of response to the acquisition of *P. cepacia* have been noted: 1) a fulminate,

rapidly fatal course, 2) a subacute course with fever, rapid decline in pulmonary function and death in 9 to 18 months, or 3) an indolent course much like that caused by other gram-negative pathogens in CF (114-116).

Other gram negative organisms such as *E. coli*, *Klebsiella species*, *Proteus species*, and serratia are isolated in a minority of patients. Their significance, if any, in clinical disease is unknown. *E. coli* and *Klebsiella ozaenae* both undergo mucoid transformation similar to pseudomonas in CF patients.

Aspergillus, most commonly *A. fumigatus*, can be cultured from sputa in up to 10 percent of CF patients. Clinical manifestations which meet the criteria of allergic bronchopulmonary aspergillosis are reported in children and adults. The incidence is not clear, but the syndrome tends to occur in patients who demonstrate reactive airways disease on pulmonary function testing (117). In one series positive aspergillus skin tests and serum precipitins were found in 67 percent of adults with CF (42). Hypersensitivity pneumonitis and invasive aspergillosis are rare complications (42, 117).

Miscellaneous pathogens

The role of anaerobic bacteria in the course of CF remains unknown. Although primary lung abscess is a rarety, reports of foul sputum that responds to antibiotic therapy is not infrequent. The recent evidence that these organisms may be cultured from aspiration of tissue specimens suggests that they may have a pathogenic capacity similar to that seen in bronchiectasis.

Colonization of the tracheobronchial tree with *Candida albicans* is seen in patients with CF who have been on long term antibiotics or high dose steroids (118). There are rare reports of invasive disease, but colonization is usually benign.

In spite of the morbidity from infectious pulmonary disease the CF lung is remarkably resistant to the tubercle bacillus. In a series of over 700 patients followed for over 18 years only 2 cases of active tuberculosis were documented (28). This phenomenon is unexplained.

The role of viral infection in pulmonary deterioration in patients with cystic fibrosis has only recently been investigated (119). Despite bacterial colonization, it has long been noted that patients with acute exacerbation of pulmonary disease lack the usual signs of bacterial infection such as fever, clinical toxicity and elevation of the white blood cell count. In a prospective study it was found that 49 CF patients had significantly more viral infections than their siblings, and the frequency of these infections correlated with pulmonary function deterioration (119). These findings have significant

implications for the use of antibiotics and warrant further investigation.

XII. Host Defense in Cystic Fibrosis

Although cystic fibrosis is a multisystem disease, lung destruction is the major cause of morbidity and mortality in the adult. Since colonization with mucoid pseudomonas is almost universal and has been reported to be the "harbinger of death", I shall briefly review recent studies which focus on the immunologic dysfunction produced by the host-bacterium interaction (120). Patients with CF with pseudomonas colonization are not immunocompromised in the way this term is usually used. Indeed, immunologic responses to antigens are excessive. Nevertheless, *P. aeruginosa* is never eliminated from the respiratory tract yet never spreads systemically beyond this site.

Adherence

P. aeruginosa has been shown to adhere poorly to normal buccal epithelial cells (121). Fibronectin is a cell surface glycoprotein that supports adherence of gram-positive bacteria but inhibits adherence of gram-negative bacteria (122). The fibronectin concentration is diminished on CF buccal epithelial cells either due to a congenital deficiency or due to digestion by the increased protease activity in CF saliva (122).

A constituent of serum, ciliary dyskinesis factor, has been described in CF patients which decreases tracheal mucous velocity and also acts as a potent chemotactant for PMN's (123). Other inhibitors of tracheobronchial clearance produced by fibroblasts and mononuclear leukocytes have been described. These and other less well described events result in mucoid *P. aeruginosa* colonizing the lower respiratory tract of CF patients.

Phagocytosis

Both neutrophils (124) and alveolar macrophages (125) of CF patients are able to ingest pseudomonads and release inflammatory products *in vitro*. CF serum is a good source of opsonins for phagocytosis of *P. aeruginosa* by PMN's and blood monocytes, but these opsonins do not facilitate phagocytosis by alveolar macrophages (126, 127). This finding suggest that macrophage phagocytosis *in vivo* may be deficient and may contribute to continued colonization.

The classic and alternative complement pathways function normally in these patients (128-130). It is unlikely that the

persistence of infection is related to a deficiency in complement function.

Immunoglobulin and Specific Antibody Production

Adult CF patients with advanced disease have markedly elevated levels of serum IgG, IgA, IgM and salivary IgA (131, 132). Antibodies to a wide range of bacterial products have been found in the sera and sputa of CF patients. These include almost every cellular and extracellular product of pseudomonas such as alkaline protease, elastase, exotoxin A, mucoid exopolysaccharide, lipopolysaccharide and outer membrane proteins (133-143). Mucoid exopolysaccharide is a B cell activator, and colonized patients are stimulated to produce a wide range of antibodies (144). The significance of these antibodies is unclear. However, patients whose precipitins increase rapidly or who have very high titers have significantly more rapid deterioration in pulmonary function and a worse prognosis (145, 146).

Immune complexes have been found in many organs and body fluids of CF patients (147). Their role as a primary or secondary cause of pulmonary destruction remains controversial. There is increasing evidence, however, that pulmonary and circulating immune complexes have a pathogenic role and are associated with increased mortality (148, 149). A recent investigation suggests that increased IgG antibody levels in association with systemic immune complexes and complement activation may contribute to a poor prognosis and may provide non-invasive markers for pulmonary destruction (150).

Bacterial and Inflammatory Cell Products

Pseudomonas elaborates toxins such as proteases, exotoxin A and leukotoxins. PMN's also release neutral proteases such as elastase, collagenase and cathepsin G during phagocytosis (151). Sputum elastase activity is increased in all patients with cystic fibrosis, but the concentration is significantly higher in patients colonized with pseudomonas (151). There is both biochemical and pathologic evidence of lung connective tissue destruction in cystic fibrosis (152, 153). Although incomplete, recent evidence suggests that pseudomonas and granulocyte proteases act synergistically in the destruction of elastin (151). These observations may explain the deterioration of pulmonary function associated with colonization with mucoid pseudomonas.

XIII. Treatment and Outcome

The treatment of pulmonary disease in CF has been emperic and symptomatic rather than specific (154) but nevertheless has

resulted in a dramatic increase in mean survival. All treatment regimens have been directed at patients who are moderately to severely symptomatic. The efficacy of any therapeutic modality in patients with mild or no symptoms has never been addressed.

Treatment of Infection

Antibiotics became generally available in the late 1940's. Table 17 presents early data on the prolonged use of tetracyclines in the treatment of CF (155).

Table 17

Continuous use of Tetracylines in
Treatment of CF: Effect on Survival

Year	Number of Patients	Average Age at Death
1940-1948	57	12.8 mo.
1949-1983	42	45.2 mo.

Survival was significantly increased from 13 to 45 months following treatment with continuous tetracyline. Subsequent studies documented a similar decrease in mortality following the use of intermittent oral antibiotics (156). Most centers used these data, recommendations from the Cystic Fibrosis Foundation and personal experience as the basis for treating CF patients with oral antibiotics for mild pulmonary exacerbations. These are defined by cough with purulent or foul sputum and a decreased level of activity. The patient may or may not have fever, an increased WBC or a change in the chest radiograph (28, 154). Antimicrobials utilized have included an antistaphylococcal agent in combination with tetracycline, trimethroprim-sulfamethoxazole, chloramphenicol or cephalexin.

Cephalexin has no activity against pseudomonas and limited activity against hemophilus and coliform bacilli. In a double blind controlled study it was found that in stable patients who are colonized with staphylococcus or hemophilus, oral therapy with cephalexin alone decreased the frequency of respiratory exacerbations, reduced patient hospitalizations and decreased bacterial colony counts of sputum (157). However, when patients were colonized with pseudomonas the clinical response to the same therapy was less salutory, and there was a tendency for colonization with a mucoid species of pseudomonas to increase (157). This study implies that an antibiotic active against *S. aureus* and other gram-positive bacteria is important in preventing acute pulmonary exacerbations of cystic fibrosis in the absence of pseudomonas.

When there is a failure of response to oral antibiotics, the patient is classified as having an acute pulmonary exacerbation. Factors precipitating this worsening are unknown, but lobar pneumonia or empyema rarely exist. Patients presenting with the changes listed in Table 18 usually respond clinically to intravenous antibiotic therapy in either a hospital (158) or home environment (159).

Table 18

Characteristics of Acute Pulmonary Exacerbations in Cystic Fibrosis

Change in volume, appearance or color of sputum
Increased respiratory rate or dyspnea
Progressive physical findings on auscultation
Decreased appetite or weight loss
Fever
Changing or new infiltrates

Acute exacerbations are almost always manifested by a change in sputum associated with an increased respiratory rate and therefore work of breathing. One or more of the following features is also present: an increase in rales and rhonchi on auscultation of the lungs, anorexia and weight loss secondary to pulmonary rather than GI symptoms, low grade fever and new or changing infiltrates on chest radiographs.

Despite lack of documentation that bacteria play an etiologic role in these exacerbations, the focus of treatment has been on the selection of antibiotics effective against pseudomonas. The aminoglycosides listed in Table 19 have formed the mainstay of treatment for many years.

Table 19

Intravenous Aminoglycoside Therapy for Patients with Cystic Fibrosis

Drug	Dosage (mgm/kg/d)	Therapeutic Peak (µg/ml)	Toxic Trough (µg/ml)
Gentamicin	7.5 - 10	8-10	>2.0
Tobramycin	7.5 - 13	8-10	>2.0
Amikacin	15.0 - 22	25-30	>6.0

The pharmacokinetics of the aminoglycosides are altered in CF, and usual doses result in subtherapeutic levels. There is a

larger volume of distribution and an increase in total body clearance in these patients (160, 161).

Doses of gentamicin and tobramycin are given every 6 to 8 hours to achieve a peak level of 8-10 µg/ml and a trough level of <2 µg/ml. In these patients the principle side effect is ototoxicty with renal toxicity occurring only with excessive trough levels. Amikacin is recommended every 8-12 hours to obtain a peak of 25-30 µg/ml and a trough of <6 µg/ml. In local practice Tobramycin has become the aminoglycoside of choice for CF patients (personal communication).

Antimicrobials listed in Table 20 are beta lactam derivities and cephalosorins that have *in vitro* anti-pseudomonas activity and *in vivo* responses when employed in the treatment of acute exacerbations of cystic fibrosis (154, 158, 162).

Table 20

Anti-Pseudomonal Antimicrobials Used
in Patients with Cystic Fibrosis

Drug	Dosage (mgm/kg/day)	Maximum Dose (gm/day)
Carbenicillin	400-600	30-40
Ticarcillin	200-400	18-24
Mezlocillin	200-400	18-24
Azlocillin	200-600	18-24
Piperacillin	200-600	12-18
Imipenem	30-90	-
Ceftazidime	150-200	-

Among the five extended spectrum penicillins, carbenicillin has the least *in vitro* activity against pseudomonas and piperacillin the greatest; the three others have roughly comparable intermediate activity (162). Imipenem demonstrates the most *in vitro* sensitivity against *P. aeruginosa* among these antimicrobials, but organisms develop resistance promptly. Ceftazidime is the most potent of the cephalosporin derivities against *P. aeruginosa* with activity approaching that of the aminoglycosides. It is also among the few antimicrobials with consistent *in vitro* activity against certain strains of *P. cepacia*.

Specific intravenous antibiotic regimens used for acute pulmonary exacerbations in CF are listed in Table 21.

Table 21

Intravenous Antibiotic Regimens Used for
Pulmonary Exacerbations in Cystic Fibrosis

Aminoglycoside alone
Aminoglycoside with anti-pseudomonal penicillin
Anti-pseudomonal penicillin alone
Anti-pseudomonal cephalosporin alone

The efficacy of any regimen is judged solely on clinical response, and assessment is confused by the addition of other treatment modalities. Pseudomonas is never eradicated from the sputum, and pulmonary functions rarely change significantly.

Tobramycin alone versus a placebo has been used in a single double blind trial in the treatment of 20 children. The authors found only a "trend toward clinical improvement" in the treated group (163).

Many combinations of aminoglycosides and anti-pseudomonal penicillins have been investigated with similar efficacies in clinical results (164-168). Studies have not shown any regimen to be impressively superior to another (162). In 1983 McLaughlin compared three regimens, ticarcillin and tobramycin, azlocillin and tobramycin and azlocillin and placebo. Clinical and bacteriologic responses were similar in the three groups leading to the conclusion that an anti-pseudomonal penicillin alone may be adequate in the treatment of acute exacerbations of CF (169).

Piperacillin as a single drug (170) and in a comparative trial of piperacillin versus piperacillin and tobramycin (171) again produced similar clinical and bacteriologic results. Pseudomonal strains with *in vitro* resistance to piperacillin did not emerge in either study using the drug as a single agent.

Imipenem/cilastatin, as a single drug regimen has recently been investigated in two studies (172, 173). Cilastatin has no antibiotic activity but prevents nephrotoxicity in laboratory animals. In both studies treatment was safe and efficacious by clinical response. However, pseudomonas strains resistant to Imipenem developed in 90 percent of patients after 2 weeks of treatment.

Ceftazidime may be as potent as Imipenem against *P. aeruginosa* and is the only antimicrobial with *in vitro* effectiveness against *P. cepacia*. It has been investigated as the only therapy in patients who did not improve clinically on other regimens; there was a 67 percent favorable response rate (174). In a comparison of ceftazidime alone versus gentamicin and carbenicillin, clinical improvement occurred in 96 percent of 50 patients treated with ceftazidime and 78 percent of 32

patients treated with the double drug regimen (175). Development of *in vitro* resistance to ceftazidime occurred infrequently in this report.

Recommendations for intravenous antibiotic therapy based on this review are presented in Table 22.

Table 22

Recommendation for Intravenous Antibiotic Therapy in Acute Pulmonary Exacerbations

Aminoglycosides alone are not adequate.

Beta lactam antimicrobials plus an aminoglycoside are not superior to the beta lactam alone.

Anti-pseudomonal beta lactam agents, especially piperacillin, are adequate therapy.

Imipenem should not be used as a single agent.

Anti-pseudomonal cephalosporins, especially ceftazidime, are adequate therapy.

Aminoglycosides probably should not be used as single agents. Although combinations of a beta lactam antimicrobial and an aminoglycoside have been the standard therapeutic regimen for acute exacerbations, there seems to be no clinical superiority over single drug regimens. However, the combination of piperacillin and tobramycin may be useful in treatment failures. The agents must be administered separately and blood levels of the aminoglycoside monitored. A beta lactam agent alone, expecially piperacillin, is adequate in patients who are not sensitive to penicillin. Imipenem should not be used as a single agent due to rapid emergence of resistant strains of pseudomonas. In penicillin sensitive patients, and in patients colonized with *P. cepacia*, ceftazidime can be recommended as a single agent.

Anti-inflammatory Drugs

Steroids are indicated in the treatment of all patients with allergic bronchopulmonary aspergillosis and in those in whom steroid responsive asthma may co-exist. In addition, a recent report suggests that steroids may alter the progression of the primary pulmonary disease (176). In a randomized, double blind, placebo controlled study, alternate day prednisone (2 mgm/kg) therapy was given to patients 1-12 years old. The treated group had a significant advantage in height, weight, vital capacity, $FEV_{1.0}$ and number of hospitalizations over the placebo group

after four years (176). The significance of this finding in the treatment of adults is not known.

Respiratory Therapy

Although respiratory therapy is usually administered to these patients the efficacy of aerosols in the treatment of CF has been questioned. No study has documented an objective benefit from inhaled antibiotics or mucolytic agents. Their use in mildly symptomatic adults is at best controversial. In patients with partially reversible airways obstruction the aerosol delivery of beta adrenergic inhaled bronchodilators is as effective in CF as in simple asthma (177).

Variable short-term results have been obtained when pulmonary function parameters are measured after a single postural drainage treatment (178). However, in patients who produce large volumes of viscid secretions postural drainage has been shown to increase mucociliary transport. Percussion and vibration with postural drainage is better than drainage alone or drainage plus cough in producing sputum. Chest physiotherapy with percussion and postural drainage is recommended for adult patients with significant secretions.

Bronchial Lavage

Bronchial lavage with either large volumes of saline or mucolytic agents was initiated in the 1960's. Subjective improvement has been reported; however, pulmonary function has been documented to decrease for 48 to 72 hours after lavage. Complications have included pneumonia and respiratory failure due to continued mobilization of very large volumes of secretions (179). This technique cannot be recommended in adult patients.

Vaccines

Pseudomonal vaccines directed at cell wall products, cellular exoproducts, attenuated live organisms, and cellular contents have been shown to result in high antibody titers, but there is no clinical efficacy (154, 180).

XII. Complications and Treatment

Pneumothorax

Spontaneous pneumothorax most often occurs in adolescent and adult patients with moderate to severe pulmonary disease. The incidence is increasing as patients live to an older age and has been reported in up to 16 percent of adult patients (181). The recurrence rate may be as high as 45 percent. An increase in

mortality within two years of a pneumothorax is attributed to the natural history of the disease (182). Small pneumothoraces are usually asymptomatic and are frequently preceded by hemoptysis attributed to rupture of a subpleural bleb. Treatment with observation or tube thoracostomy is similar to any patient with a pneumothorax. The high incidence of recurrence suggests treatment by pleural sclerosis with drugs or thoracotomy with pleurectomy after the first episode (181).

Hemoptysis

The incidence of hemoptysis is also increasing with mean survival. Minor episodes of hemoptysis are reported in greater than 60 percent of patients (29). Massive hemoptysis occurs in 6 percent and is most common between the ages of 18-21 years (29, 183). Massive hemoptysis occurs only in patients with severe pulmonary disease who are colonized with pseudomonas, most commonly during an acute exacerbation of pulmonary symptoms (183). When hemoptysis does not cease spontaneously, the current recommendation is for immediate bronchoscopy to localize the bleeding site followed by bronchial embolization (180). The results of this procedure are an 88 percent success in stopping bleeding, a 23 percent recurrence rate, and a 1.6 percent complication rate of inadvertently embolization of spinal arteries (184-186).

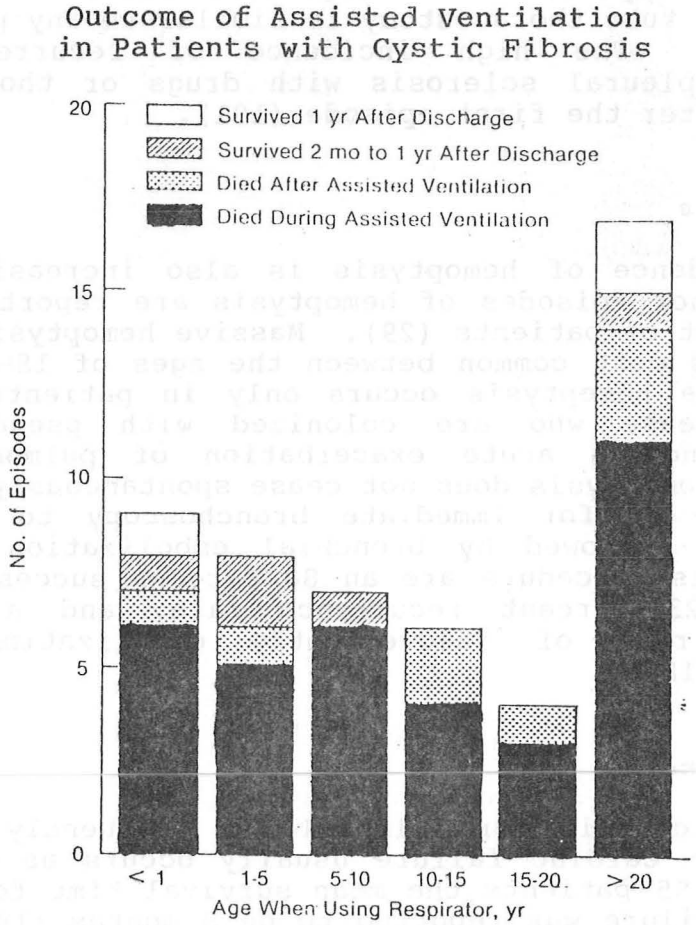
Cor pulmonale

Although chronic cor pulmonale is frequently present, the onset of overt cardiac failure usually occurs as a preterminal event. Among 55 patients the mean survival time following right ventricular failure was reported to be 8 months (187). Although therapy is unsatisfactory, the emphasis is directed at improving the underlying pulmonary status and improving oxygenation by the use of low flow oxygen (188).

Respiratory Failure

Progressive airways obstruction, sputum production and ineffective cough ultimately result in CO_2 retention and respiratory failure. Hypercapnia may be rapid in onset secondary to acute infection or develop more slowly, usually in association with signs of right heart failure. If there is no improvement with oxygenation, antimicrobials, chest physiotherapy and endotracheal suction, endotracheal intubation and assisted ventilation must be considered. The results of assisted ventilation in patients with cystic fibrosis (189) are considerably worse than the results in other forms of chronic obstructive lung disease (190, 191). Figure 12 presents the combined outcome of patients from 9 different cystic fibrosis centers (189).

Figure 12



Sixty-nine percent of patients with respiratory failure died after 1 to 395 days of mechanical ventilation, and an additional 12 percent died in the hospital 1 to 42 days following assisted ventilation. Only 3 (6%) patients survived longer than one year. Based on these results patients with cystic fibrosis should not be considered candidates for mechanical ventilation except in the rare instance of a patient with good baseline function in whom acute respiratory failure develops due to a rapidly reversible cause (189).

XIII. Summary

Only recently has it been realized that cystic fibrosis has a spectrum of severity which allows some patients to reach adult life with few or no symptoms. Young adults with chronic pulmonary symptoms, severe rhinitis with polyps or nasal obstruction, nonspecific abdominal complaints or a chest radiograph with

upper lobe interstitial infiltrates and large lung volumes deserve further investigation. Additional history may include previous abdominal surgery, excessive sweating or complaints of infertility. A mucoid strain of *Pseudomonas aeruginosa* obtained on sputum culture is probably adequate for diagnosis. Confirmation of cystic fibrosis is obtained by the demonstration of an elevated sweat chloride on a properly performed laboratory determination. Treatment in adult patients may be minimal and is related to the pulmonary symptoms. For acute exacerbations, antimicrobials should be administered. The necessity for genetic and fertility counselling may be the most important undertaking in this age group.

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