Chapter 3

Medical Aspects

Contents

Page

PATHOLOGY **69**
- Respiratory System **69**
- Gastrointestinal System **70**
- Reproductive System **71**
- Sweat Glands **71**
- Skeletal System **72**

DIAGNOSIS **72**
- Sweat Test **72**
- Immunoreactive Trypsin Test **72**
- DNA Analysis **73**

TREATMENT AND PROGNOSIS **73**
- Medical Management **73**
- Chest Physical Therapy **76**
- Lung Transplants **77**
- Prognosis **77**
- Psychological Aspects **78**

SUMMARY AND CONCLUS1ONS **79**

CHAPTER PREFERENCES **79**

Box

3-A. Cystic Fibrosis Therapies on the Horizon 76

Figures

3-l. Organ Systems Affected in Cystic Fibrosis 70
3-2. Distribution of Cystic Fibrosis Centers in the United States 74
3-3. Median Survival of U.S. Cystic Fibrosis Patients Over Time 77
3-4. Age Distribution of U.S. Cystic Fibrosis Patients in 1990 78

Tables

3-l. Sweat Chloride Levels in Normal and Cystic Fibrosis-Affected Individuals 72
3-2. Medications Used in Management of Cystic Fibrosis 75

Chapter 3
Medical Aspects

For a ***17th*** century mother, tasting salt on her baby's brow portended death; according to folk wisdom of the period, the infant was hexed. Modern medicine now recognizes this as an indicator of cystic fibrosis (CF), the most common, life-shortening, recessive genetic disorder among Caucasians. CF also occurs in other races, but at a 4- to 36-fold lower incidence. A multifaceted condition, CF compromises many functions throughout the body, but varies from patient to patient in severity of symptoms and the extent to which different organs are affected. No cure exists for CF, but treatment of the digestive and respiratory symptoms lengthens lifespan considerably.

While the devastating consequences of CF have been apparent for centuries, an understanding of its underlying mechanisms is relatively new. Since the 1940s, doctors and scientists have known that CF is a heritable condition—i.e,, one transmitted from parents to children through their genes. New scientific developments have revealed the nature of the genetic defect and offer insight into the relationship between genetics and disordered function, clearing the way to increased comprehension of the manifestations of CF and better management of the condition. Today, new therapeutic possibilities for affected patients exist, as well as technologies to detect people who are asymptomatic carriers of CF mutations.

This chapter provides an overview of the medical principles important to understanding the context of carrier screening for CF. It describes CF's manifestations, outlines how the condition is diagnosed, and summarizes methods of treatment. Additionally, this chapter looks forward, considering new medical techniques that could improve therapy and prognosis for people with CF.

PATHOLOGY

CF affects the respiratory, gastrointestinal (GI), and reproductive systems, as well as the sweat glands. Although the disorder is present at birth in affected persons, the symptoms vary among individuals. Approximately 10 percent of people with CF are born with a detectable intestinal blockage called meconium ileus. In general, diagnosis occurs by age ***3,*** although some individuals do not develop symptoms until later in childhood, adolescence, or even adulthood (10,15,54,62).

CF generally involves dysfunction of exocrine glands, the glands that secrete into ducts or onto specific organ surfaces. Exocrine glands include lacrimal (tear) glands, sweat glands, and part of the pancreas. Mucus-producing cells lining the respiratory and GI tracts are also part of the exocrine system. Although specific glands are impaired to differing degrees, CF affects both major classes of exocrine glands-the serous and mucous types. In CF, secretions from serous glands have an increased salt content. In contrast, secretions from mucous glands have a normal or diminished salt content, but the disorder causes them to be thicker than normal secretions, leading to obstruction of the gland's ducts (49).

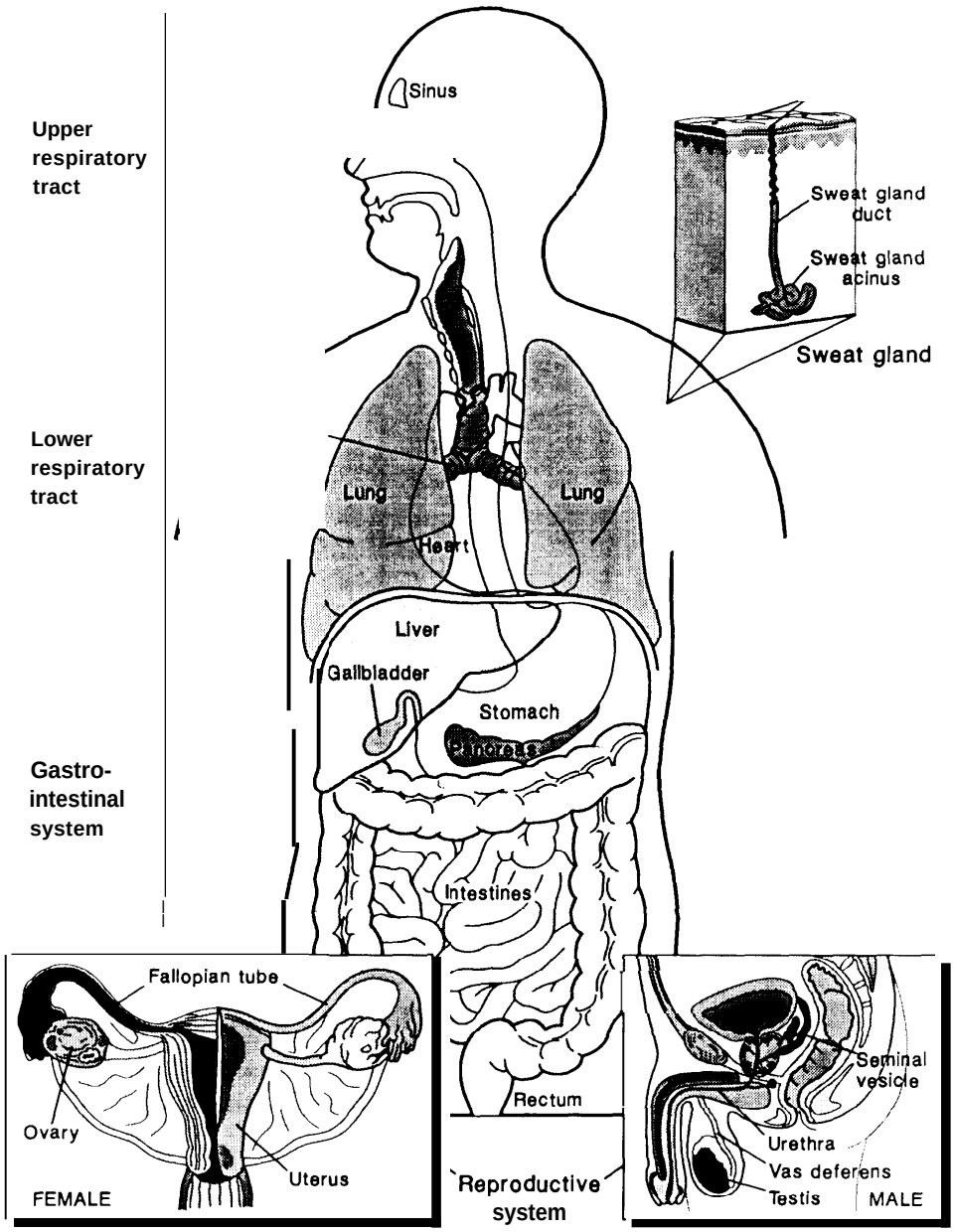
Respiratory System

CF affects both the lower respiratory tract (the lungs) and the upper respiratory tract (the nose and sinuses), although the upper tract is less involved (figure 3-l). CF produces thick, sticky mucus that obstructs breathing passages and interferes with normal gas exchange and removal of bacteria, viruses, and other particles from the airways. Thus, individuals with CF often suffer chronic lung infections, followed by inflammation, then subsequent lung damage (8,24,30,54). What often begins as coughing and wheezing can progress over time to shortness of breath, limited lung function, chronic lung infections, and numerous pulmonary complications that often include respiratory and heart failure.

Three types of bacteria, *Staphylococcus aureus, Haemophilus influenzae,* and *Pseudomonas aeruginosa,* generally colonize the lungs of CF patients. The former two are usually the frost bacteria found in CF-affected bronchi, while *Pseudomonas* more frequently occurs as the disease progresses. ***Pseudomonas*** infection poses additional problems because it is often resistant to antibiotics.

The severity of respiratory problems often determines the quality of life and survival of CF patients (15,37,54). At one extreme, some infants develop chronic lung obstruction and infection soon after

Figure 3-l-Organ Systems Affected in Cystic Fibrosis



SOURCE: Office of Technology Assessment, 1992.

birth, resulting in impaired pulmonary function and early **death.** Other patients experience only mild symptoms, living several decades before they succumb to progressive lung disease and heart failure.

Gastrointestinal System

Digestive difficulties are common in CF and often predominate over respiratory symptoms early in life. The pancreas, liver, gallbladder, stomach, and intestines can be affected, but if treated properly the problems generally are not life-threatening (figure 3-l).

About 85 to 90 percent of individuals with CF experience some pancreatic problems, primarily because inadequate quantities of pancreatic enzymes are released to digest food (22,54). As in the

lugs, overly thick secretions are produced by the exocrine pancreatic ducts. Digestive enzymes are trapped, leading to destruction of pancreatic tissue and preventing the enzymes from reaching the intestines, where they are needed for digestion. Poor nutrition and impaired growth result because food—particularly fat and protein-is not broken down appropriately and cannot be absorbed by the body.

Nutritional status and pulmonary disease appear related; adequate nutrition helps alleviate the symptoms of pulmonary disease, whereas poor nutrition reinforces pulmonary disease and worsens the prognosis (37,54). The inability to digest fat interferes with intestinal absorption of fat-soluble vitamins—A, D, E, and K. Vitamin deficiencies lead to complications such as impaired blood clotting and scaly skin. Resticted protein digestion also causes serious problems, including edema in infants due to lack of blood proteins. Insufficient release of pancreatic enzymes can cause large, greasy, malodorous stools, abdominal pain or discomfort, and excessive gas.

Pancreatic manifestations also include diabetes and pancreatitis, although both are less frequent complications than exocrine pancreatic insufficiency. Diabetes, rare in CF patients under age 10, occurs in 10 percent of patients between ages 10 and 20, and is found in an additional 10 percent with each decade thereafter. CF-associated diabetes is mild compared to juvenile-onset diabetes; it tends not to cause the severe manifestations seen with the latter disease, such as nerve lesions and skin ulcers. Pancreatitis, inflammation of the pancreas, occurs in 1 percent of CF patients (54).

In the GI tract and associated organs, thick mucus accounts for many of CF's clinical signs. As mentioned earlier, meconium ileus occurs in 10 percent of newborns with CF. In these babies, meconium (fetal stool) obstructs part of the small intestine, the distal ileum. Older CF patients can develop a condition akin to meconium ileus--distal intestinal obstruction syndrome-where intestinal contents either partially or completely block the intestine (10,54,62).

CF patients suffer, less frequently, two additional GI complications: intussusception, or the folding of a piece of the intestine within itself, and rectal prolapse, or projection of the rectum through the anus (10,54). Finally, the liver is generally unaffected, although biliary cirrhosis<caused by blockage of the ducts that transport bile into the intestine—and fatty liver can occur, generally late in the course of the disease (10,54). In 1990, liver complications caused death in approximately 4 percent of people with CF (27).

Reproductive System

CF manifests itself in the reproductive systems of males and females (figure 3-l); for both, sexual development can be delayed. CF damages the Wolffian duct, the embryological precursor of the male reproductive organs, in 95 percent of CF-affected males (10). The vas deferens is often absent (57), incompletely formed, or blocked by mucus, resulting in an effect similar to vasectomy. Additionally, sperm might be improperly formed in men with CF (39,65). As a result of these factors, only **2** to **3** percent of CF males are fertile (10). DNA analysis of men with congenital absence of the vas deferens reveals that many with this disorder might have CF, although they have no apparent symptoms of CF other than infertility (5).

In women with CF, thick, dehydrated mucus centaining abnormal electrolytes often plugs the opening to the uterus, impeding sperm migration and reducing the pregnancy rate. Additionally, women patients can develop amenorrhea secondary to pulmonary disease and poor nutritional status, further reducing the chances of conception. Fertility in women with CF is estimated at 2 to 20 percent; this figure, however, might bean underestimate as many women with CF use contraceptives (10, 15,27,42,54). In patients with advanced lung disease, the physical strain of pregnancy poses a health risk. Nevertheless, with proper care, increasing numbers of women with CF are successfully having children. Women with milder symptoms tolerate pregnancy better than those with advanced lung disease.

Sweat Glands

CF also manifests in the sweat glands of affected individuals (figure 3-l). Patients lose excessive amounts of salt in their sweat, predisposing them to episodes of salt depletion. Although not a major concern for children and young adults—who can take salt tablets to compensate-infants can suffer form potentially fatal salt loss, particularly during periods of warm weather (10,54,62).

Skeletal System

Skeletal system problems occur in some CF patients, probably secondary to the pulmonary and digestive malfunctions. Many-but not all—children with CF are short in stature and also have a delayed growth spurt. Other skeletal affects include joint pain, spine curvature (kyphosis), and clubbing (swelling) of fingers and toes (10,54,62).

DIAGNOSIS

Physicians combine clinical criteria and laboratory tests to diagnose CF. Early signs and symptoms can include recurrent wheezing, persistent cough and excessive mucus, recurrent pneumonia, intestinal obstruction, low weight gain despite normal eating (failure to thrive), abnormal bowel movements, rectal prolapse, salty taste to the skin, nasal polyps, and enlargement of the fingertips. Since many childhood ailments share symptoms with CF and since its symptoms vary in severity from individual to individual, CF is often undiagnosed or misdiagnosed (10,15). Physicians identify some newborns before they develop symptoms through assays performed because of a family history of CF. Family history of CF also contributes to diagnosis for older individuals.

Sweat Test

The sweat test is the most common method for confirming CF. CF affects exocrine glands, including sweat glands. In these glands, excess sodium (Na^+) and chloride (Cl-) ions are lost to the sweat. This indicator was frost discovered in 1953; by 1959, it was being used to diagnose CF (29).

To measure the salt content in the sweat of an individual, sweating is induced by placing apilocarpine-soaked gauze pad or falter paper on the person's arm or back. (Pilocarpine activates sweat glands.) A low electric current is passed through the area (iontophoresis) for 4 to 6 minutes to drive the pilocarpine into the sweat glands. Next, the skin is cleaned and a sterile, preweighed, dry gauze pad is taped to it. Sweat is collected for up to an hour to obtain an adequate amount (100 mg), then the pad is weighed and sweat volume deterrnined. Finally, the sweat is rinsed out of the pad and the pad weighed to ascertain salt content. Elevated Cl^- levels confirm a diagnosis of CF (17) (table 3-l). The testis generally repeated in positive cases, as well as in borderline or negative cases where symptoms still strongly suggest CF. Some laboratories measure both Na^+ and Cl^- content in sweat.

Table 3-l--Sweat Chloride Levels in Normal and Cystic Fibrosis-Affected Individuals

Sweat chloride (mmol/L)	Status
<40	Normal
40 to 60	Borderline
>60	Presumptive case of CF

SOURCE: Office of Technology Assessment, 1992.

Although painless and of moderate expense, the sweat test has several drawbacks. As with all diagnostic tests, accuracy depends on how the testis performed and interpreted. Pilocarpine iontophoresis is difficult to perform on newborns under 8 weeks of age, making sweat testing in newborns difficult. Moreover, complications of CF—such as edema (swelling)---or recent use of corticosteroids can confound the results. Other conditions also yield elevated Cl^- levels in perspiration, although these can generally be distinguished from CF by their symptoms. Additionally, normal adults, in rare instances, have increased levels of Cl^- in their sweat. One study found approximately 40 percent of persons referred to CF centers were sent there as a result of false sweat test results by the initial tester (10). Though the sweat test is imperfect, when performed properly and considered in conjunction with typical clinical findings, it can be used to diagnose CF with better than 98 percent accuracy (9). Increasingly, DNA analysis is used to establish a positive CF diagnosis in people with borderline sweat test results (68).

Immunoreactive Trypsin Test

A protocol for newborn CF screening, the immunoreactive trypsin (IRT) test, measures levels of pancreatic trypsin, a digestive enzyme (13,54). In newborns with CF, obstruction of the exocrine pancreatic ducts causes this enzyme to backup into the circulatory system. In the IRT test, a drop of blood is isolated on a card, dried, and chemically analyzed to detect elevated levels of the enzyme (71). This use of dried spots—known as "Guthrie spots' '—parallels the method of newborn screening for a range of genetic disorders (e.g., phenylketonuria and hypothyroidism) performed by a number of States (4).

While sweat testing is intended to be diagnostic, the IRT test is not. The IRT test yields a higher

number of false positives (unaffected individuals incorrectly suggested to have CF) and false negatives (affected individuals incorrectly identified as not having CF) than the sweat test (7,55). For this reason, it requires followup with other procedures for conclusive diagnosis,

Current pilot studies combine the use of the IRT test with other tests to enhance its diagnostic value. In a Colorado study, the false positive rate of IRT alone was reduced by sequential use of the IRT test with a stricter threshold and the sweat test (34,36). Programs in Wisconsin, Pennsylvania, and Australia combine the IRT test with followup DNA analysis for a single mutation, known as DF508 (53,56,70). The efficacy of presymptomatic identification of the disease in newborns remains uncertain (1,36).

DNA Analysis

Both sweat testing and IRT analysis measure phenomena secondary to the genetic cause of CF. In contrast, DNA analysis directly examines the genetic material, DNA, to reveal whether an individual has CF mutations. Currently, DNA analysis is used for prenatal detection, carrier screening, and, increasingly, determining the status of borderline cases (3,68). DNA analysis has also been used in combination with the IRT test for newborn screening (56,70).

As detailed in chapter 4, more than 170 different mutations cause CF, complicating prospects for routine diagnosis using DNA assays. While direct analysis of DNA is theoretically the most precise diagnostic test, at present it can only be used to diagnose positive cases. Due to the number of different mutations—many of which are not included in test panels-DNA analysis cannot confirm that a person does not have CF. However, DNA-based CF mutation tests, while not yet ready for sole use as a diagnostic test in negative cases, are accepted as conclusive in positive cases. In its 1991 patient registry, the Cystic Fibrosis Foundation (CFF) accepted positive results from DNA tests without requiring sweat test confirmation (68). (Chapter 4 discusses the correlation of molecular diagnosis with clinical outcome.)

TREATMENT AND PROGNOSIS

The goal of CF treatment is to maintain a stable condition for long periods of time and allow affected individuals to lead relatively normal lives. General therapy involves home treatment, with occasional hospital stays as needed. The regularity of hospitalization varies with the individual, and ranges from infrequent to once every 2 to 3 months, often increasing in frequency in the last few years of life. Treatment seeks to control infection, promote mucus clearance, and improve nutrition.

The daily therapeutic regimen for a person with CF depends on the severity of the disease, but the principal components of treatment focus on managing the pulmonary and digestive manifestations of CF. Even in asymptomatic cases, regular visits to a physician are generally advised to prevent problems and to detect early problems when complications do arise. Today, treating CF has become increasingly specialized. Currently, more than 110 major clinical centers and a number of satellite centers and outreach clinics are devoted to delivering CF care (16,17) (figure 3-2). The CFF, founded in 1955, has played a large role in advancing CF treatment and care.

Medical Management

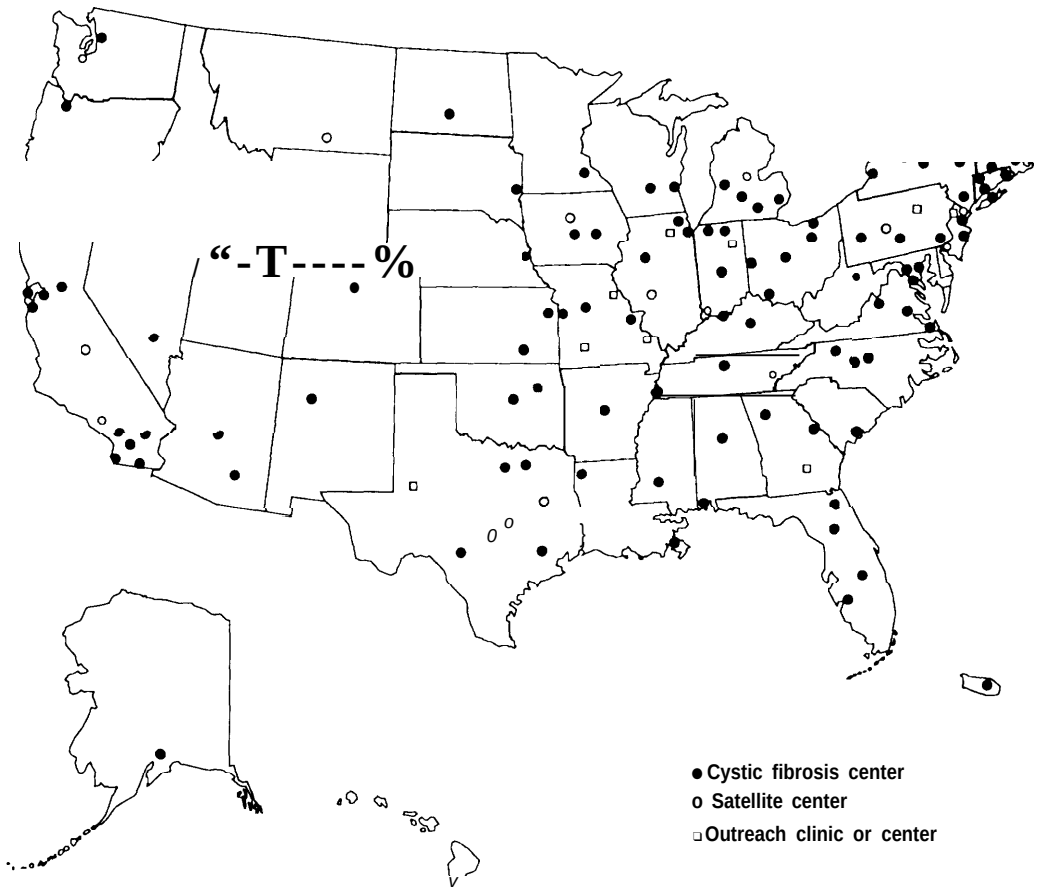
Medical management of CF focuses on:

- alleviating blockage in the airways,
- fighting lung infection,
- managing airways inflammation, and
- facilitating proper nutrition.

Lung Therapy

Lung therapy for CF requires both medical and physical approaches. Medical management of lung-related problems involves the use of aerosols, bronchodilators, corticosteroids, and antibiotics (table 3-2). Aerosols deliver medications and water to the lower respiratory tract; most use a saline solution as the vehicle. Mucolytics, agents (generally N-acetyl cysteine) designed to break up mucus, can be used in aerosol form, Efficacy and safety of currently available mucolytics are controversial, but new mucolytics under development might prove safer and more appropriate for routine use. Bronchodilators are also used to reverse airway obstruction. These drugs are delivered by aerosol, injection, or orally. Bronchodilators used to treat CF include metaproterenol, isoetharine, and albuterol. In some instances, physicians prescribe corticosteroids to treat allergic reaction to a fungus that grows in CF airways. Long-term corticosteroid therapy is not generally beneficial (9). Finally, nonsteroidal anti-inflammatory medications for CF therapy are cur-

Figure 3-2—Distribution of Cystic Fibrosis Centers in the United States



SOURCE: Office of Technology Assessment, 1992.

rently being evaluated. Most of these treatments involve some degree of controversy as to efficacy and long-term safety (11,25,64).

As with all therapies, each of these treatments is useful in some patients and not in others. In some patients, for example, currently available mucolytic aerosols induce cough, cause bronchospasm, and promote inflammation; bronchodilators, while often providing immediate relief of symptoms, might not be effective in long-term use and could even prove harmfud. Short-term use of corticosteroids in adults can cause detrimental effects such as immune system suppression, hyperglycemia, and glycosuria-requiring their use be evaluated on a patient-by-patient basis (25).

In contrast to the use of aerosols, bronchodilators, and corticosteroids (which ameliorate the physiological effects of CF on the lung), antibiotic treatment reduces or eliminates infection, thus slowing inflammatory responses that can lead to progressive lung disease. Unlike other therapies, antibiotic treatment is not controversial. The major antibiotics for countering CF-related infections include the penicillins and the aminoglycosides (e.g., gentamicin). Quinolones (e.g., ciprofloxacin and norfloxacin), cephalosporins, and other antibiotic families are also used. Antibiotics can also be aerosolized.

Treatment with antibiotics varies from intermittent use to repeated, sustained use. CF patients often need much larger doses than persons without CF. As with all long-term antibiotic treatment, bacterial resistance to treatment is a major problem. While antibiotic therapy is generally provided on an outpatient basis, hospitalization is sometimes necessary. Lengths of stay vary, but can range as long as 2 to 3 weeks. Hospitalization allows more careful management of patients, as well as the use of antibiotics that must be given intravenously. The

Table 3-2—Medications Used in Management of Cystic Fibrosis

Type of medication	Purpose
Antibiotics	**Fight bacteria in lungs**
Penicillins	
penicillin	*Streptococcus*
ampicillin	*Haemophilus*
ticarcillin	*Pseudomonas*
piperacillin	*Pseudomonas*
methicillin	*Staphylococcus*
Cephalosporins	
cephalexin, cephaclor	*Streptococcus, Staphylococcus, Haemophilus*
ceftazidime	*Pseudomonas*
Tetracyclines	*Streptococcus, Staphylococcus, Haemophilus, Pseudomonas*
Erythromycin	*Streptococcus, Staphylococcus, Haemophilus*
Chloramphenicol	*Staphylococcus, Haemophilus*
Sulfa drugs (e.g., sulfisoxazole, trimethoprim-sulfamethoxazole)	*Haemophilus*
Aminoglycosides (e.g., gentamicin, tobramycin, amikacin)	*Pseudomonas*
Quinolones (e.g., ciprofloxacin, norfloxacin)	*Pseudomonas*
Aztreonam	*Pseudomonas*
Bronchodilators	**Open air passages, facilitate breathing**
Theophyllines	
β-agonists (e.g., albuterol, metaproterenol, isoetharine)	
Cromolyn	
Corticosteroids	
Mucolytics	**Dissolve mucus**
N-acetyl cysteine	
Digestive enzymes	**Digest food**
Dietary supplements	**Maintain nutrition**
Vitamins A,D,E,K,	
High-calorie supplements	
Diuretics	**Stimulate kidneys to remove water; relieve fluid accumulation throughout body; ease pumping burden on heart**

SOURCE: Office of Technology Assessment, 1992, based on D.M. Orenstein, Cystic *Fibrosis:A Guide for Patient and Family(New* **York NY: Raven Press, Ltd., 1989).**

necessity of hospitalization, however, remains controversial. Recent evidence indicates that less expensive home intravenous treatment could be as effective as identical hospital-based treatment if the patient complies. Although antibiotics are standard treatment, the method of delivery, selection of particular antibiotics, and the usefulness of prophylactic treatment are debated. Finally, in addition to aerosols, bronchodilators, corticosteroids, and antibiotics, several new methods to manage CF are foreseeable (box 3-A).

Digestive **Therapy**

Digestive therapy for CF has several goals—achieving ideal weight, insuring normal growth and maturation, sustaining respiratory muscle strength, and maintaining adequate immunity. The major components of digestive therapy are pancreatic enzyme replacement, administration of fat-soluble vitamins, and dietary supplementation.

For pancreatic enzyme replacement therapy, extracts of animal pancreas are ingested orally. Replacing pancreatic enzymes enables CF patients to properly digest food and absorb nutrients. Enzymes must be taken each time a person eats. Dietary supplementation is important to compensate for increased energy needs associated with CF. Many people with CF need approximately 150 percent of normal caloric intake. Recommended supplements are high-calorie, consisting of high-protein foods, medium-chain triglycerides, and simple carbohydrates. In severe cases of malnutrition or during acute periods of lung infection, nasogastric feeding or total parenteral nutrition can be necessary.

Box 3-A-Cystic Fibrosis Therapies on the Horizon

Standard CF pulmonary treatments of the past few decades focused on fighting infection and clearing mucus in the airways, but new therapies target preventing the process of infection and subsequent inflammatory response (12,19). These therapies attempt to intervene at specific junctures in the disease process by:

. decreasing the viscosity of lung secretions;
. protecting the airway from destruction and preventing infection;
• correcting the ionic imbalance; and
. compensating for the genetic defect through gene therapy.

Two promising drugs-DNase and amiloride-thin CF lung secretions through different mechanisms. Both are in clinical trials for approval by the U.S. Food and Drug Administration (FDA) (42,58). DNase is an enzyme that breaks down DNA that accumulates from the debris of inflammation-fighting cells in the lungs of CF patients. DNase loosens CF mucus in vitro and in vivo, and is safe for short-term use (2,38,60,61); long-term studies are underway (58). In short-term studies, patients using DNase show noticeable improvement in breathing ability, suggesting that it might be an effective CF therapy in the near future (40). Company officials anticipate that DNase might be on the market in early 1993 (6). Amiloride is a diuretic that loosens lung secretions by blocking sodium ion reabsorption (43). Clinical trials demonstrating safety and efficacy of its use in aerosol form are in progress (42). The FDA has announced plans to streamline its drug approval process, a decision that could make treatments such as DNase and amiloride commercially available soon (69).

Ironically, the body's natural infection fighting mechanism contributes to the massive destruction of airways in CF patients. Substances known as antiproteases can protect the airway epitheliums from injury caused by innate bacterial defense substances. Included in this category are alpha-l-antitrypsin, secretory leukocyte protease inhibitor, and a compound known as ICI 200,880, all undergoing clinical trials for FDA approval (8,42,51).

Other potential therapies circumvent the environment that leads to infection and subsequent buildup of cells. These new therapies attempt to correct the ion imbalance characteristic of CF (ch. 4). Administration of adenosine triphosphate and uridine triphosphate in conjunction with the diuretic arniloride stimulates chloride ion (Cl^-) secretion, and could mitigate the effects of decreased Cl^- conductance in individuals with CF; FDA clinical studies are in progress (42,44). Recent in vitro evidence that proper chloride conductance can be induced in some CF cells by applying large doses of cyclic-AMP-stimulating drugs suggests this as a future avenue for pharmaceutical intervention (18,20,73).

Unlike treatments that attack symptoms of CF, gene therapy is designed to rectify the deficits of the disease by directly altering DNA. In theory, new DNA can be inserted into faulty cells to compensate for the genetic defect. Gene therapy for CF (discussed in greater detail in ch. 4) is in the animal experiment stage at present. Using a crippled virus specific to airway epithelial cells, the normal human CF gene was administered directly to the lungs of rats by aerosol spray. After 6 weeks, the transferred DNA continued to function (14,59). Aerosolized liposomes, fatty capsules that can transport drugs directly into cells, have been used to deliver alpha-1 -antitrypsin genes into rabbit lungs, and a similar mechanism might be used to deliver the CF gene to the lungs (35). Despite significant experimental progress, however, many hurdles remain for CF gene therapy to be feasible in humans. Long-term safety of the procedure needs to be demonstrated and questions need to be answered regarding the most appropriate means of transfeming the gene, the number of cells that need to be corrected, and the duration of treatment.

SOURCE: Office of Technology Assessment, 1992.

Chest Physical Therapy

The cornerstone of CF treatment is chest physical therapy (PT) to move the mucus that blocks major air passages out of the lungs (10,15,54). Bronchial drainage, also called postural drainage, is a specific form of chest PT commonly used for CF, and involves turning the body in various positions to align air passages in the lung to optimize the effect of gravity. It is usually performed leaning on a table or lying over a couch. Either the individual or an assistant (e.g., a professional therapist or a family member) claps on the chest or back to loosen mucus while the patient coughs it up. Mechanical percussors and vibrators can facilitate PT. People with CF generally require PT one to four times daily, depending on their clinical status. When flareups in CF symptoms or acute infection occur, the frequency of chest PT generally increases. In light of the time commitment required to accomplish PT-at least once a day for 20 minutes or longer—compliance is often poor.

Lung Transplants

Since the 1980s, two new options have become available to treat the terminal stages of CF: heart-lung and double-lung replacement surgery (23,26,47,66). Through 1991, 140 heart-lung transplants have been performed in CF patients internationally, with 89 patients still alive (26,47). Since 1986, 58 double-lung transplants have been performed in CF patients; 40 patients were surviving in 1991 (26). As with all organ transplantation, rejection is the major obstacle to survival. Availability of donor organs and cost are also limiting factors. When lungs were available, the operation and aftercare cost approximately $200,000 in 1989 (47).

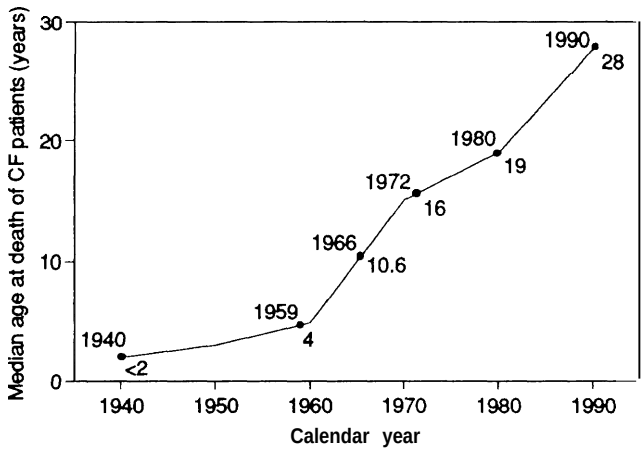
Heart-lung transplant was pioneered first, and appears better suited for CF patients with right heart failure. Double-lung transplants are increasing in frequency (66), and they appear to reduce the incidence of acute and chronic infection. While the sputum of CF patients after transplant can become colonized with *Pseudomonas* bacteria, it generally clears in the succeeding months (47,66). Since most CF patients do not require new hearts, leaving the original heart intact avoids coronary artery disease associated with rejection of the transplant. It also removes the CF patient from the competition for donor hearts (31,47).

To be considered for transplant therapy, a patient must be a nonsmoker who has no signs of other systemic or pleural disease, does not take high doses of steroids, is within 15 percent of ideal weight, and has an emotionally supportive family (23,26,47,66). Neither approach can cure CF: Both types of transplants leave the pancreatic, GI, reproductive, and sweat gland manifestations of CF unresolved.

Prognosis

Survival data for individuals with CF change rapidly (figure 3-3), Fifty years ago, most infants born with CF died within the frist 2 years of life. In 1959, the median age at death was 4 years. Median age at death has increased one year per year for the past decade (33). In 1990, the median age at death had progressed to 28 years-meaning that one-half of babies born with CF in 1963 were alive in 1990 (27,28). The CFF reports that estimating the life expectancy of an infant born with CF today would require data from considerably more years than have been collected and is thus not feasible (52). Some research indicates past improvements in survival might not continue without further advances in therapy: Data from Canada show a plateau in median survival age at 28 years over the last decade (21). Nevertheless, a few postulate median survival of an infant born in 1992 with CF might be 40 years (12).

Figure 3-3-Median Survival of U.S. Cystic Fibrosis Patients Over Time

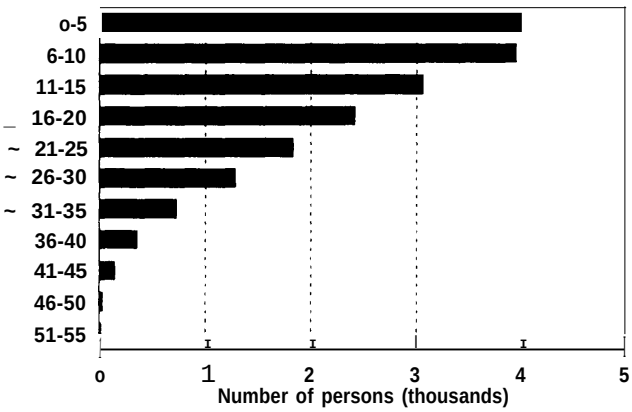


SOURCE: Office of Technology Assessment, 1992, based on S.C. FitzSimmons, "Cystic Fibrosis Patient Registry, 1990: Annual Data Report," Cystic Fibrosis Foundation, Bethesda, MD, January 1992; and S.C. FitzSimmons, Cystic Fibrosis Foundation, Bethesda, MD, personal communication, February 1992.

Three medical factors account for the increased life expectancy of persons with CF: the advent of antibiotics in the 1940s, the introduction of chest PT in the 1950s, and advances in nutrition in the 1970s and 1980s. Past failure to diagnose mild cases of CF also probably negatively skewed median survival data. And, the development of CF centers providing specialized and comprehensive care likely has contributed to longevity. Currently, people with CF can often lead full lives for long periods and can pursue college educations, maintain careers, marry, and have families.

As noted earlier, CF follows a varied clinical course. A few affected babies die from meconium ileus within the first days of life, while some people can be largely asymptomatic for 10 years (figure 3-4). Certain prognostic factors help predict survival. Lung function measured by a clinical test helps predict short-term survival, particularly when considered with respect to age and gender (41). Mortality rates in children and adolescents are higher than in adults with similar measured lung function (41). Likewise, mortality rates are higher in females than males with comparable lung function (41). In general, males live a few years longer than

Figure 3-4-Age Distribution of U.S. Cystic Fibrosis Patients in 1990



SOURCE: Office of Technology Assessment, 1992, based on S.C. FitzSimmons, "Cystic Fibrosis Patient Registry, 1990: Annual Data Report," Cystic Fibrosis Foundation, Bethesda, MD, January 1992.

females (27). Africa.n Americans have more difficulty during the early years of life, but fare better than Caucasians later (10). Psychosocial aspects of the disease also affect prognosis. Denial, dependence, and depression-on the part of either parent or patient-result in poor compliance with therapeutic regimens and poor prognosis. Other signs of poor prognosis include respiratory complications before age 1, abnormal chest x-ray at diagnosis, or inadequate nutritional status. Clinically mild symptoms at the time of diagnosis and pancreatic sufficiency both predict longer survival (10). Certain CF mutations associate with severe lung disease, while others cause milder forms (9,67,72).

The effect of early diagnosis on clinical outcome is unclear, and whether neonatal screening for CF is useful remains controversial. Some clinical experience supports the belief that earlier diagnosis, and hence earlier treatment, improve prognosis. However, when and where patients are treated has a significant effect on outcome (10). Long-term data from neonatal screening programs in Colorado and Wisconsin could settle this issue (1,34,36,70).

Psychological Aspects

Beyond physical ailments, people with CF and their families experience emotional and social effects. As in any chronic illness, being sick adds additional strain to life. In particular, because CF requires daily treatments-even mildly affected individuals require digestive enzymes and usually chest PT---the disease affects the daily lives of the affected person and his or her family. Psychological response to the demands of the disease and outlook on life vary considerably (45,50,63). Not all individuals with CF and their families experience all-or even most—negative emotional aspects of the disease; in particular, those with milder cases grow up with little disruption to their lives. Specific feelings and reactions, however, typify particular periods in both the life of the individual and the course of CF (15,54,62).

Children, adolescents, and adults with CF react differently to the condition, Children sometimes resist home care, such as chest PT, because it intrudes on play time and interferes with their desire for independence. Children can be sensitive to being different from their peers, and can be embarrassed by physical manifestations of the disease such as flatulence, coughing, and dietary restrictions. Missing school due to frequent lung infections or hospitalizations interferes with school work; hospitalization can be a stressful and frightening experience. Children above age 10 start worrying about the seriousness of CF and the possibility of death, feelings that are exacerbated when they see friends succumb to the disease (48,62).

CF accentuates the fears, conflicts, and insecurities associated with adolescence. At a time when they most want to be independent of their parents, teenagers with CF frequently depend on them for daily chest PT and other medical necessities. Some teenagers refuse to take enzyme supplements or medication to rebel against parental attempts to keep them healthy. The short stature, delayed onset of secondary sex characteristics, and sometimes impaired athletic ability characteristic of CF can be traumatic for adolescents who feel acutely aware of their bodies and seek peer approval. Nonetheless, many teenagers with CF are as psychologically healthy as their peers (15,50,54,62).

As the prognosis for CF improves, it increasingly becomes a disease of young adulthood rather than a disease of childhood (figure 3-4). Due to the progressive nature of CF lung complications, many adults are physically more restricted than they were as children. If they go to college, young adults with CF must factor the demands of daily chest PT, often performed by family, into the decision of where to attend. CF also influences career choice, since individuals face frequent bouts of infection and can be limited in physical activity. The need for health

insurance also can shape job choice (ch. 8). The threat of early death influences family planning and marriage decisions as well. Within the medical community, a need exists for increased attention to CF care of adults, whose medical and psychological concerns differ from those of children (17,46,48,54,63).

For the family of a child with CF, the disease often shapes family time and interactions (54,62). With the initial diagnosis, family members experience a range of emotions: anger, shock, and grief that their child has a life-threatening illness; denial of the disease; relief to finally know definitely what is wrong and what can be done (15,48,54,62). Having a child with CF can cause conflicts in marriage and social life. CF is time consuming, can limit family vacations, and demands that parents have jobs that provide adequate health insurance. For siblings, CF can inspire resentment of the attention focused on the sick child. When a sibling with CF dies, siblings can feel guilt that they were responsible (15,48,54,62).

While the burden of CF can be emotionally difficult, many individuals and their families persevere, leading full lives. The medical condition is only part of the social context and environment that creates the whole life. Since studies focus on the negative impact of CF, it is much easier to enumerate the difficult parts of the experience than it is to document that many CF patients and families are happy (15,62). For them, CF is just a part of life. As one mother of a son with CF notes, no one—with or without CF—is guaranteed a ‘ ‘perfect life or a perfect child” (32).

SUMMARY AND CONCLUSIONS

CF is the most common, life-shortening, recessive genetic disorder among Caucasians. Age of diagnosis and severity of symptoms vary greatly from individual to individual. CF generally involves exocrine gland dysfunction. It affects multiple organ systems in the body, including the lungs, digestive tract, reproductive organs, and sweat glands, as well as the skeletal framework. The condition wreaks its most severe toll, however, on the respiratory and digestive systems, where it is characterized by chronic obstruction and infection of the airways and insufficiency of the pancreas in providing digestive enzymes. Ultimately, the majority of people with CF die from heart failure stemming from the respiratory consequences of CF.

Diagnosis of CF usually follows from its clinical symptoms, with confirmation by laboratory tests. Currently, analysis of sweat is the simplest and most reliable method for confirming CF. Measurement of a pancreatic enzyme, trypsin, is used—imperfectly—to identify CF. DNA-based CF mutation tests are not yet ready as the sole diagnostic test in negative cases, but can be used to accurately diagnose positive incidence.

Treating CF focuses on managing the respiratory and digestive symptoms to maintain a stable condition, At present, lung obstruction is ameliorated by daily chest PT and is sometimes augmented by aerosols, bronchodilators, and corticosteroids. Antibiotics are used to fight infection. The drugs DNase and amiloride, currently in clinical trials, offer hope of attenuating obstruction as well, although they will not be a substitute for chest PT To attain adequate nutrition, pancreatic enzyme replacement and dietary supplementation are required. In a few end-stage cases, double-lung or heart-lung replacement alleviates CF-related pulmonary complications, although digestive difficulties remain and rejection of the transplanted organs can limit longevity.

Research into the underlying basis responsible for CF progresses at a rapid pace. In the coming decade, new approaches to therapy, including amiloride and nucleotide triphosphates, could decrease lung damage by combating primary manifestations at the level of ion transport. Treatments that correct the molecular deficit rather than ameliorating symptoms seem feasible. Eventually, gene therapy to supplement the gene itself could be possible.

Over the past half-century, CF has evolved from an illness nearly always fatal in childhood to one in which numerous individuals now survive into adulthood. Currently, the median survival age is 28 years. Advances in new therapies and comprehensive approaches to patient care have all contributed to longer lives for people with CF. The search for new treatments, and ultimately a cure, might improve future prognosis.

CHAPTER 3 REFERENCES

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