Centennial Review

Cystic Fibrosis Since 1938

Pamela B. Davis

Department of Pediatrics, Case Western Reserve University School of Medicine at Rainbow Babies' and Children's Hospital, Cleveland, Ohio

Cystic fibrosis (CF) was distinguished from celiac disease in 1938. Then, it was a pathologic diagnosis, life expectancy was approximately 6 months, and the autosomal recessive disease was believed to arise from abnormal mucus plugging exocrine ducts. Death often occurred from lung infection. Discovery of the sweat electrolyte defect in 1953 and standardization of the sweat test in 1959 allowed identification of milder cases, and CF was no longer considered only a disorder of mucus. In 1955, establishment of centers with programs of aggressive, comprehensive care initiated striking improvement in longevity. The pillars of care established then (attention to nutrition, airway clearance, treatment of lung infection) remain today. In 1983, chloride transport was identified as the basic physiologic CF defect, accompanied by increased sodium reabsorption. In 1980, we learned that inflammation contributes independently to lung disease and constitutes an independent therapeutic target. In 1989, the discovery of the CF gene demonstrated the basic defect to be in a cAMP-regulated chloride channel. This afforded new diagnostic tests, opportunities for research, and prospects for using the gene as therapy. Since then, substantial advances in basic and clinical research catalyzed therapeutic improvements: median survival age now exceeds 30 years. The Cystic Fibrosis Foundation center network provides not only opportunity to conduct clinical trials but also means to disseminate new therapies. In the future, treatments directed at the basic defect can be expected, with concomitant improvements in morbidity and mortality.

Keywords: cystic fibrosis; *Pseudomonas aeruginosa*; sweat test

DESCRIPTION OF THE DISEASE

Cystic fibrosis (CF) was first recognized as a separate disease entity in 1938 when autopsy studies of malnourished infants distinguished a disease of mucus plugging of the glandular ducts, termed "cystic fibrosis of the pancreas," from others with celiac syndrome (1). This disease was characterized by malabsorption of fat and protein, steatorrhea, growth failure, and pulmonary infection. Pancreatic damage and lack of pancreatic enzyme secretion accounted for nutritional failure, which was assumed to lead to vulnerability to lung infection, often the terminal event. The thick, sticky mucus clogging the ducts of mucus glands throughout the body gave rise to the alternative designation "mucoviscidosis" (2). The disease became known as a "generalized exocrinopathy," because many exocrine glands were affected (3). CF was recognized to be genetic in origin and transmitted in an autosomal recessive pattern (4). At that point, studies on the basic defect focused on abnormalities in mucus. A critical discovery was made during the 1948 heat wave in New York by an astute young pediatrician, Paul di Sant'Agnese, who noticed that many of the infants presenting with heat prostration had CF. He postulated that their sweat was abnormal, and went on to demonstrate a fivefold excess of sodium and chloride in the sweat of patients with CF, which persisted in patients with CF after the heat wave subsided (5). This consistent CF abnormality apart from mucus glands implied that the basic defect could not be in mucus, mucus modification, or macromolecular secretion. Elevated sweat chloride concentration offered a convenient diagnostic test. The pilocarpine iontophoresis technique of Gibson and Cooke (6) rendered such testing practical. Few tests in clinical medicine have the discriminating power of the "sweat test." Nearly every patient with a clinical diagnosis of CF has elevated sweat chloride concentration, and only a few conditions, clinically quite distinct from CF, produce elevated sweat electrolytes (Figure 1). With the sweat test, milder patients, some without pancreatic insufficiency, could be identified. In 1983, sweat ducts were used by Paul Quinton to identify chloride transport as the basic defect in CF (7). About the same time, Knowles and coworkers (8) and Boucher and colleagues (9) identified increased sodium reabsorption as a regular feature of CF in the airways. When the CF gene was discovered in 1989 (10–12), its identity was verified using cells derived from sweat duct. This gene encodes a cAMP-regulated chloride channel, the CF transmembrane conductance regulator (CFTR). Nowadays, the term "cystic fibrosis" applies to patients with a lesion in a cAMP-regulated chloride channel, CFTR, that is expressed in many epithelial cells, including sweat duct, airway, pancreatic duct, intestine, biliary tree, and vas deferens, which can give rise to elevated sweat chloride concentration, lung disease characterized by bacterial infection and bronchiectasis, pancreatic insufficiency, intestinal obstruction, biliary cirrhosis, and congenital bilateral absence of the vas deferens, often in combination. Lesions in CFTR can give rise to other clinical syndromes or vulnerabilities as well (Figure 2), but most clinicians will reserve the term CF for those who will ultimately develop progressive, fatal lung disease.

DIAGNOSIS

CF was initially a pathologic diagnosis. After the sweat test came into general use, the diagnosis of CF was made on the basis of a sweat chloride concentration of 60 mEq/L or greater plus either a sibling or first cousin with CF, or lung disease of appropriate character, or pancreatic insufficiency (13). To be reliable, the sweat test must be performed in centers that meet national standards, and where many such tests are done by experienced technicians. A second positive test is required to confirm the diagnosis. A few patients with CF have normal sweat chloride concentrations. For these patients, testing for the presence of

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Correspondence and requests for reprints should be addressed to Pamela B. Davis, M.D., Ph.D., Department of Pediatrics, Case Western Reserve University School of Medicine at Rainbow Babies' and Children's Hospital, BRB 8th floor, 2109 Adelbert Road, Cleveland OH 44106. E-mail: pamela.davis@case.edu

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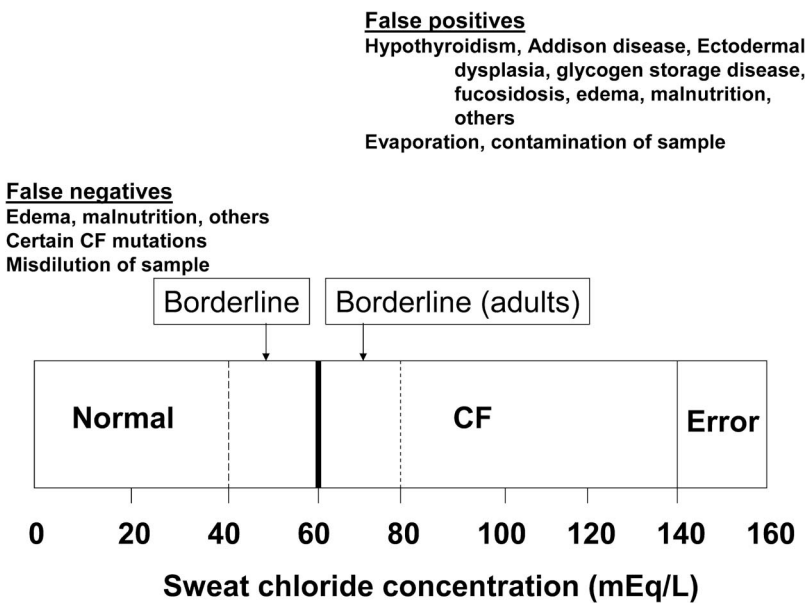

Figure 1. Sweat chloride concentrations related to cystic fibrosis (CF) diagnosis. Revised and reprinted by permission from Davis PB. Cystic fibrosis. *Pediatr Rev* 2001;22:257–264.

sperm in the semen in men (nearly all male patients with CF are azoospermic), assessment of liver and gall bladder function, identification of pansinusitis, evidence of intestinal obstruction, or measurement of nasal potential difference (NPD), as discussed below, may be helpful (14).

After 1989, when the CF gene was identified (8–10), the diagnosis could be made by direct identification of two mutant CF alleles. Commercial testing for the 86 most common alleles will identify about 93% of patients with CF. However, because there are by now more than 1,000 CF alleles reported (the list is found at http://www.genet.sickkids.on.ca/cgi-bin/WebObjects/MUTATION), it is possible to miss a rare mutation. Genetic testing can also be applied to prenatal diagnosis. Often, the mother is tested, and if she is positive, the father is tested. When both parents are known to be heterozygous for a CF allele, amniocentesis or chorionic villus sampling can retrieve fetal DNA to determine the genotype of the fetus.

For patients with a highly suggestive clinical syndrome in whom the diagnosis is still in doubt, NPD evaluation can be helpful. In 1981, Knowles and colleagues (15) reported that the NPD was abnormal in patients with CF compared with healthy and diseased control subjects and identified sodium reabsorption as part and parcel of the CF diathesis. NPD measurement is now progressing from a research tool to a clinical test. Patients with CF have elevated sodium reabsorption and reduced chloride secretion in response to cAMP. This pattern can be diagnostic; however, this test requires considerable skill, a bank of normal and typical CF results for comparison, and experienced interpretation.

Increasingly, patients are identified by newborn screening. Already, 17 states are performing or will soon implement newborn screening. Immunoreactive trypsin levels, measured in blood spots collected at birth, are elevated in most patients with CF (16), but the cutoffs that capture nearly all patients with CF also capture five to six times that number of babies who do not have CF. Therefore, immunoreactive trypsin screening is often followed by screening for CF mutations or a second immunoreactive trypsin test. Definitive diagnosis still depends on either sweat testing or identification of two mutant alleles, however, and one must take care not to dull the suspicion of CF in older children and even adults in the proper clinical setting, since screening will not identify every patient.

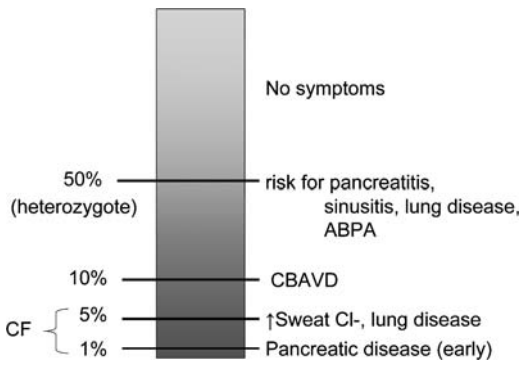

Figure 2. CF transmembrane conductance regulator (CFTR) activity related to clinical manifestations. ABPA = allergic bronchopulmonary aspergillosis, CBAVD = congenital bilateral absence of the vas deferens. Revised and reprinted by permission from Davis PB. Cystic fibrosis. *Pediatr Rev* 2001;22:257–264.

The CF Gene

The discovery of the CF gene by positional cloning in 1989 (8–10) was a tour de force by three research groups, those of Lap-Chee Tsui and Jack Riordan at the Hospital for Sick Children in Toronto, and Francis Collins at the University of Michigan. Although the gene for chronic granulomatous disease was identified by positional cloning earlier, the CF gene was the first to be found by positional cloning whose function was entirely unknown. Having the gene in hand allowed more refined diagnosis of CF, better insight into the clinical problems, and the definition of the impact of partial deficiency of its protein product, the CFTR. It also provided researchers with the means to define downstream effects of CFTR deficiency and the nature of CF mutations, and to screen for drugs to correct them. The gene itself became a potential therapeutic agent. It is difficult to overestimate the importance of this discovery.

The CF gene resides on chromosome 7, is some 250 kB in length, and encodes a protein of 1,480 amino acids, CFTR.

Nearly everyone with the distinct clinical syndrome of CF has a lesion in this gene, and the most common of more than 1,000 disease-causing alleles, ΔF508, accounts for 70% of CF chromosomes in the United States. Mutations vary in the severity of disease they produce. Patients with at least one "mild" CF allele retain some chloride channel activity, so pancreatic function may be sufficient for digestion, the lung disease is less severe, and the sweat chloride concentration may even be in the normal range (17, 18). Patients with CFTR mutants that give rise to about 10% of the normal level of CFTR mRNA may have normal sweat chloride concentrations, normal lung function, normal pancreatic function (i.e., no clinical CF) but, if they are male, suffer congenital bilateral absence of the vas deferens (19). Persons heterozygous for a CF allele appear to be at increased risk for pancreatitis, sinusitis, or allergic bronchopulmonary aspergillosis (Figure 2) (20–23).

About 50% of American patients with CF are homozygous for the ΔF508 mutation, and even among these patients with the identical genes at the CF locus, there is a wide range of disease severity. Therefore, environmental, therapeutic, and other genetic influences may contribute to the outcome of the CF disease. Studies that identified exposure to tobacco smoke (24) or poor socioeconomic status (25) as having adverse effects on outcome are important in guiding clinical advice and social policy. Aggressive treatment regimens matter, although the exact "best" regimen is not yet proven. Even when these factors are controlled, there are still inherent differences among patients in the CF disease process, and a survey for modifier genes is underway (26, 27).

CLINICAL SYNDROME

Before the discovery of the ion transport defects in CF in the early 1980s, the firmest intellectual foundation for understanding the disease lay in its clinical description. The findings of basic research must be consistent with the clinical picture, and clinical insights allowed effective symptomatic therapy to be developed. Even after the identification of the basic defect, the description of the clinical syndrome represents a critical and valuable body of knowledge.

Lung Disease

Lung disease is the major cause of morbidity and mortality in CF. At first it was believed that lung infection was a consequence of severe malnutrition, so it was a major conceptual advance to think of lung disease as an independent component of the CF disease process (28). Pathologic studies indicate that, at birth in CF, the lung is normal, or nearly so: widening of the mouths of submucosal glands, as if the glands were already impacted with mucus, was the only abnormality detected before infection (29). This is a critical observation, for it allows hope that, with early postnatal therapy directed at the basic defect in the lung, fatal disease can be prevented. In contrast, the pancreas and the gut are often damaged at birth. Like normal infants, patients with CF acquire viral infections, which are not more frequent but are more likely to be symptomatic (30). Unlike normal infants, patients with CF develop bacterial infections early in life, which initially appear to clear with vigorous antibiotic therapy. Later, however, permanent colonization of the airways is established. It is likely that colonization occurs because reduced chloride secretion and increased sodium reabsorption in airway epithelium leads to reduced water content of secretions as well as reduced depth of periciliary fluid, which in turn lead to trapping of inhaled bacteria and slower clearance (31). Some, but not all, studies suggest that the airway surface fluid of patients with CF has reduced capacity to kill bacteria, although the mechanisms of this failure are unclear (32). Early in life, a spectrum of bacterial invaders is detected, including *Staphylococcus aureus* and *Haemophilus influenzae* (33). Eventually, however, *Pseudomonas aeruginosa* appears and, after years in the CF lung, acquires a mucoid phenotype and forms a biofilm in the lung, an event marked by acceleration in the decline of pulmonary function (34). Infection incites an exuberant, persistent neutrophilic inflammatory response, and the neutrophil and bacterial products ultimately destroy the airway wall. Moreover, there is increase in volume of glands and secretory cells in the epithelium: their secretions contribute to airway impaction. Bronchiectasis ensues, and the growth of blood vessels that accompanies it predisposes to massive hemoptysis. With time, a modest degree of emphysema develops. Bronchial cysts can develop and reach the periphery of the lung, predisposing to pneumothorax (35). Bacterial infection persists and periodically exacerbates, requiring treatment. Despite intensive therapy, infection is difficult to eradicate. Over time, more resistant organisms supplant the initial invaders. Atypical mycobacteria, yeast, and fungi are common. Allergic bronchopulmonary aspergillosis occurs in 2 to 16% of patients with CF, and more than half of adolescent and adult patients with CF have *Aspergillus fumigatus* cultured from the sputum (36).

Some of the antibiotic-resistant bacteria that invade the CF lung, like *Stenotrophomonas maltophilia*, appear statistically to have little impact on the course of the disease (37), but others, like *Burkholderia cepacia*, can be devastating (38). In the early 1980s, *B. cepacia* appeared in patients with CF, causing death within 1 year for about one-third of infected patients, compared with only 8% of patients matched for age and sex who did not acquire this organism. At first, there was confusion over how the organism was acquired (39), since conventional wisdom was that patients with CF did not transmit their infecting organisms to others. However, one center concluded that person-to-person transmission was likely and separated infected patients from contact with noninfected patients. The incidence of new infections fell dramatically in the first year after cohorting began (40). Subsequent studies confirmed the person-to-person mode of spread (41, 42). In fact, other organisms, including *P. aeruginosa*, are now suspected to be transferred from patient to patient, and good infection-control practices are a cornerstone of responsible management of centers (43). This will be increasingly important as more infants with CF are identified at birth to ensure that care of newly diagnosed infants in centers does not hasten acquisition of *P. aeruginosa* (44).

TREATMENT

In the mid-1950s, patients with CF began to assemble into centers for care, so physicians became familiar with the clinical manifestations of the disease and gained experience with treatment. In 1954, at the CF center in Cleveland, Leroy Matthews instituted a comprehensive program of care that attacked every complication aggressively. Matthews and coworkers (45) established three pillars of treatment: nutritional repletion, relief of airway obstruction, and antibiotic therapy of the lung infection. Over the next few years, results were dramatic. Survival and quality of life improved, all without knowledge of the CF basic defect. Although the details have changed, aggressive treatment remains the foundation of care today. In 1955, the Cystic Fibrosis Foundation was founded. One of its greatest achievements has been the establishment, accreditation, and support of a network of centers that are committed to high-quality, evidence-based care. Moreover, the foundation supports a center network for clinical research to obtain the clinical evidence necessary to make good therapeutic decisions. The center system then allows rapid

dissemination of new findings. All these factors have improved national survival considerably.

Pillar 1: Nutritional Repletion

More than 85% of patients are pancreatic insufficient at birth and others gradually lose function over time. Treatment with pancreatic enzyme supplements prevents some of the malnutrition. In the late 1980s, pancreatic enzyme supplements were reformulated as enteric-coated microspheres to survive gastric acid and dissolve in the intestines (46, 47). However, releasing large doses of active enzymes lower in the gut also predisposes to fibrosing colonopathy (48). Because both intestinal and pancreatic bicarbonate secretion are impaired in CF, even large doses of pancreatic enzymes do not fully correct malabsorption, because the pH of intestinal contents is never sufficiently alkalinized to reach the pH optimum for the enzymes. Some physicians administer blockers of gastric acid secretion to minimize acidification in the stomach (49). Fat malabsorption leads to special problems with the fat-soluble vitamins, A, D, E, and K, which must be specifically supplemented. Moreover, failure of enzyme secretion may not be the sole cause of nutritional deficits. Patients with CF also have abnormal enterohepatic circulation of bile, increased caloric demand due to severe lung disease, and the anorexia that often accompanies chronic disease. Nutritional supplementation is often necessary, from calorie-dense oral supplements to enteral feedings. Nevertheless, even now, about 20% of children with CF and over 40% of adults nationwide are classified as having nutritional failure. Relative underweight is a negative prognostic indicator. Whether correction of underweight will improve the prognosis, however, has not been rigorously shown. It is clear that underweight is associated with, and indeed can predict, poor pulmonary function (50), and provides a rationale for vigorous nutritional repletion.

Pillar 2: Relief of Airway Obstruction

A striking feature of CF is the plugging of airways with thick and sticky airway secretions, a combination of mucus and pus. Therefore, clearance of secretions assumed a prominent role in therapy early in the history of the disease. Humidification, by aerosol and mist tent, was part of the initial comprehensive care program, but later was shown to be ineffective. However, postural drainage and clapping (the "ketchup-bottle method") was effective (51) and remains the method of choice for younger patients and those too sick to cooperate with active clearance methods. Newer devices have been brought to clinical use to assist in clearance. A mechanical vest that inflates and deflates rapidly vibrates the chest and does not require a partner. Small hand-held pipelike devices into which the patient blows vibrate the airways to shake loose adherent mucus, provide back pressure to retain the airways open and prevent collapse, and have proven quite successful in expelling mucus (52). Autogenic drainage, in which breathing is controlled to expel mucus, is also effective. Healthier patients can augment clearance with aerobic exercise, which stimulates deep breathing and cough.

Drugs to improve sputum clearance have been developed by biotechnology. The sticky properties of the mucus are determined by multiple components, including free DNA, polymerized actin, and the mucins themselves, all of which are highly viscous. Cleaving free DNA into smaller pieces reduces its viscosity. Recombinant DNA technology made it possible to produce human DNase, a new drug developed specifically for CF, which is much less likely than the bovine enzyme to be immunogenic, gives minimal adverse effects, and produces improvement in pulmonary function and reduction in the number of exacerbations (53). In the last year, the simple and inexpensive strategy of hypertonic saline aerosols has been shown to result in modest increase in pulmonary function and reduction in exacerbations as well, presumably by temporarily drawing water into the airway to dislodge the mucus (54).

In CF, the airway lumen is compromised not only by secretions but also by airway edema, smooth muscle hypertrophy, and bronchoconstriction. Inhaled steroids, although never proven effective in CF in controlled clinical trials, may reduce airway edema. Bronchodilators such as β-adrenergic agonists or theophylline, intended to relax airway smooth muscle, are routinely administered, although not all patients respond to them in direct testing, and some actually have paradoxical decreases in pulmonary function (probably because when the airway wall has been sufficiently damaged, they may be held open largely by muscle tone).

Pillar 3: Treatment of Airway Infection

Culture-specific antibiotics have been a mainstay of CF therapy for 60 years (28). Still, the optimal strategies of therapy are not established. Most clinicians agree that infection accompanied by increased lung symptoms or decline in pulmonary function should be treated, although once chronic colonization is established, eradication of bacteria is not a reasonable goal. For mild exacerbations, oral therapy may be sufficient. A great improvement recently has been the development of oral antibiotics with efficacy comparable to intravenous antibiotics, such as the quinolone family for *Pseudomonas*, and linezolid for *S. aureus* (55, 56). Moreover, formulation of antibiotics for aerosol use allows the patient to achieve high antibiotic concentrations in sputum while minimizing systemic adverse effects. Despite these advances, severe exacerbations, or those that have occurred in rapid succession, require treatment with intravenous antibiotics. The appropriate duration of such therapy has not been established. Studies are now in progress to determine whether vigorous suppressive therapy in infancy, before chronic infection is established, will delay colonization and benefit the patient, without selecting for resistant organisms (57).

The benefits of suppressive therapy in the absence of symptomatic or functional deterioration were long debated but no large clinical studies were published until 1993, when a randomized trial of tobramycin specifically formulated for aerosol use demonstrated that administration of such therapy in alternate months over a 6-month period led to improved pulmonary function and fewer exacerbations (58). More antibiotic aerosol formulations are currently being developed specifically for patients with CF. Continuous oral azithromycin therapy was recently shown to benefit older patients infected with *Pseudomonas* (59), but whether this is due to its antimicrobial activity or to its antiinflammatory properties is not clear.

Suppression of Inflammation—a Fourth Pillar of Therapy

Originally, the intense inflammation in the CF lung was considered an appropriate response to infection. However, in 1980, Matthews and colleagues (60) observed that some patients with CF have very low IgG levels, and surprisingly, rather than being vulnerable to bacterial infection, they were remarkably healthy. This changed our thinking about inflammation and led to the concept that a vigorous host response might be harmful in CF. Later studies showed that infected infants with CF have higher neutrophil numbers and interleukin-8 levels in bronchoalveolar lavage fluid compared with infants who do not have CF, even when controlled for burden of bacteria (61, 62), and other studies suggest that inflammation may actually precede infection (63). Suppression of inflammation pharmacologically, either by alternate-day steroids or by high-dose ibuprofen, reduced the rate of decline of pulmonary function in young, healthy patients with CF (64, 65). Unfortunately, alternate-day steroids were associated with unacceptable rates

of growth failure, cataracts, and diabetes (66). Ibuprofen, which shows greater improvement in rate of decline of pulmonary function, also has fewer adverse effects, but is associated with increased incidence of gastrointestinal hemorrhage (67). Alternatives are needed.

Lung Transplantation

When the therapeutic armamentarium loses its effectiveness, and respiratory failure looms, life can be extended by lung transplantation. The first lung transplant was performed in 1983: more than 100 patients with CF receive new lungs each year, according to the CF Foundation Data Registry. The supply of organs limits this option, however, and many patients die on the waiting list. Survival is about 80% at the 1-year mark, and by 4 years is less than 50%, so this is not yet a perfect therapy. New data suggest that inhaled cyclosporine will improve these statistics.

DESCRIPTION AND TREATMENT OF OTHER COMPLICATIONS

Although most patients succumb to lung disease, a few patients with CF die of liver disease. The severe progressive liver disease in CF usually consists of obstructive biliary cirrhosis, characterized by eosinophilic concretions in the bile ducts and portal hypertension. However, hepatic steatosis also occurs in CF, often before nutritional repletion has been accomplished. In addition, gallstones are frequent, occurring in as many as 15% of patients. Usually the stones nucleate about a nidus of mucus, but are otherwise largely cholesterol stones. Two strategies ameliorate the liver disease: treatment with ursodeoxycholic acid and liver transplantation.

CFTR is normally expressed abundantly in the gut, and in the absence of its normal function, intestinal obstruction can develop. Presumably, fluid secretion into the gut is reduced by the absence of CFTR, and the intestinal contents have reduced water content and become inspissated. In the neonatal period, this is known as meconium ileus, and later in life, as distal intestinal obstruction syndrome. Occasionally, a bit of stool adheres to the bowel wall and provides a lead point for intussusception. These complications used to be surgical conditions, but now are most often treated with Gastrografin enemas, or even, for distal intestinal obstruction syndrome, by oral administration of osmotic laxatives. Gastrografin enemas draw water into the gut and dislodge stool that has become adherent to the bowel wall.

In most patients with CF, the pancreas is already compromised at birth. Concretions in the ducts prevent enzymes from entering the gut and digesting food. Blockage of these enzymes may incite an inflammatory response, as well as autodigestion of the gland itself. In some patients, in whom some function remains, pancreatitis may be a presenting symptom. Pancreatic insufficiency causes nutritional depletion, and requires attentive treatment with extra calories, exogenous pancreatic enzymes, and vitamins, as described above. Progressive pancreatic disease and scarring compromise the pancreatic islets, and CF-related diabetes is frequent in older patients. More than 12% of patients older than age 13 have insulin-dependent diabetes, and the prevalence increases with age. Because other hormones, like glucagon, are also compromised, this diabetes rarely presents as ketoacidosis, but hyperosmolar complications and late organ system complications, such as retinopathy or neuropathy, are sometimes observed. Steroids accelerate the need for insulin, and diabetes contributes negatively to the prognosis.

Reproductive complications of CF are nearly universal in men, because of congenital bilateral absence of the vas deferens. Early in life, the vas deferens becomes blocked by viscid secretions and is resorbed, leaving the patient with no vas deferens. Some patients come to medical attention when the vas is noted to be absent on routine examination or at herniorrhaphy. Women with CF have thick cervical mucus that fails to undergo the usual midcycle thinning, which may impair fertility. In addition, women who are markedly underweight may have irregular hormonal cycles. However, many women with CF become pregnant and, provided the patient has moderate to good lung function at the outset and is able to gain weight appropriately during the pregnancy, can carry to term and deliver healthy infants. Genotyping the father reduces the risk of producing a child with CF, and otherwise the incidence of other birth defects is not increased.

The sweat defect in CF, because of the excessive salt loss, predisposes to metabolic alkalosis and heat prostration, which is a medical emergency.

In the airway, the sinuses are regularly affected by CF. Nearly every patient in the United States has opacification of all the sinuses on X-ray, but only a minority of patients are symptomatic. Some centers fear reinfection of transplanted lungs from the bacteria harbored in the sinuses, and perform antrostomies and vigorous hygiene before transplantation.

THE CHANGING DEMOGRAPHICS OF CF

When CF was first described, the lives of the patients were short and painful. However, as milder cases were recognized, antibiotics came into wide use, pancreatic enzyme supplements became available, and patients gathered into centers where aggressive symptomatic care was practiced, both duration and quality of life improved (Figure 3). Further refinements of conventional care continue to drive median survival age upwards. Nowadays, although children with CF can expect to take multiple pills and aerosols daily, eat extra food, exercise vigorously, and incur medical costs upwards of $25,000/year, they usually remain out of the hospital, go to school, and live fairly normal lives. As the patient ages and disease advances, hospitalizations become more frequent and home therapy more extensive. More than 35% of patients with CF are now older than 18 years, and this number is increasing each year. With increased emphasis on fitness (a positive predictor of survival), attention to infection control, and continuing improvements in treatment, the trend toward an aging CF population should continue. Older patients with CF finish school, join the workforce, pay taxes, marry, start

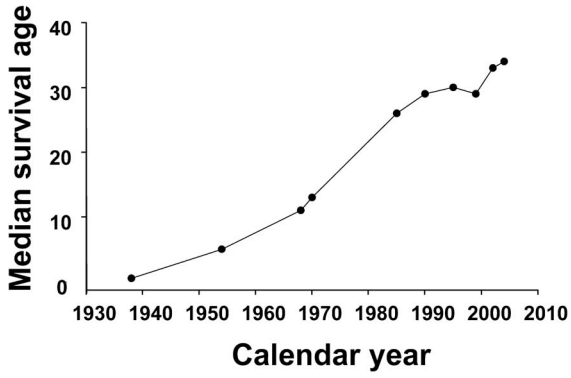

Figure 3. Median survival age for patients with CF at various times since the first description of CF. Data before 1970 are gleaned from then-current literature. Data since 1985 are from CF Foundation Data Registry and represent projections of median survival age for a child born in that year with CF.

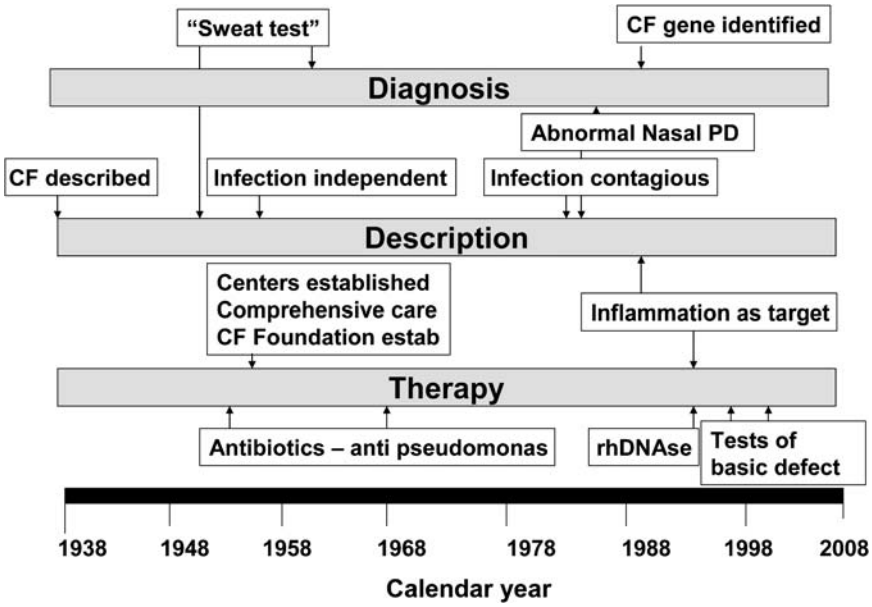

Figure 4. Discoveries relevant to diagnosis, clinical description, and therapy of CF. PD = potential difference.

families, and generally take on the problems of everyday life. As patients age, they sometimes suffer diseases common in other adults, such as hypertension or depression, and some "adult" diseases, such as gastrointestinal cancers, are more frequent in CF. The caregivers for patients with CF now include internists, obstetricians, and urologists, in addition to pediatricians and the respiratory therapists, nurses, dieticians, and social workers who have always been bulwarks of CF care.

THE NEXT HUNDRED YEARS

The life expectancy for patients with CF has improved markedly, from about 6 months to more than 30 years, without any treatments that depend on specific knowledge of the basic defect (Figure 3). Although refinements of conventional, symptomatic therapy will continue, and probably be enhanced by the clinical engineering so popular nowadays, great leaps in survival will require entirely new approaches to therapy. In 1989, the discovery of the CF gene (Figure 4) (10–12) stimulated exciting work defining the nature of the basic defect. It stands to reason that attacking the basic defect, especially early in life before permanent lung damage has set in, has the best chance of aborting the pathophysiology of CF in the lung, extending and improving life. Three approaches have been proposed: (*1*) circumventing the CF-related ion transport defects pharmacologically, by inhibiting excess sodium reabsorption and increasing chloride secretion; (*2*) using allele-specific therapies to correct the specific defects in mutant forms of CFTR, such as drugs to improve processing of ΔF508 or drugs to promote skipping of premature stop codons; and (*3*) using gene therapy, inserting a normal copy of the CF gene into the appropriate cells. Developing these approaches has required extensive basic and clinical investigation, which has been catalyzed by support from the Cystic Fibrosis Foundation and the National Institutes of Health, particularly the National Institute of Diabetes and Digestive and Kidney Diseases and the National Heart, Lung, and Blood Institute. The clinical value of potential specific "magic bullets" is yet to be proven, but progress toward phase 3 testing continues. The Cystic Fibrosis Foundation has taken the lead in encouraging the pharmaceutical and biotechnology industries to turn attention to CF. Their participation is vital if new therapies are to be brought to patients. More than two dozen therapies at various stages of clinical trials are now listed on the website of the Cystic Fibrosis Foundation (www.cff.org), a dozen of them directed at the basic defect, and this site is updated regularly as the studies progress. One likely requirement for full success of treatments directed at the basic defect is identification and treatment of patients at birth, before lung damage occurs. CF should be greatly ameliorated in the next decade, at least for patients whose lungs are clear enough to benefit. When the next centennial edition is written, perhaps we can relegate the lung disease of CF to an historical curiosity.

***Conflict of Interest Statement*:** P.B.D. has patents dealing with therapeutics potentially relevant to CF, including gene transfer, targeted gene transfer, therapeutic fusion proteins, and peptide activators of CFTR. These patents have been licensed to Copernicus Therapeutics, Inc., in which she holds equity. In 2002, her laboratory received $100,000 from Copernicus for sponsored research on gene targeting. Some patents have been sublicensed to Arizeke, from which she received royalties in 2002, and on whose scientific advisory board she served in return for $16,700 in 2004. She has served as consultant to Genzyme and Centocor in the last 3 years for sums less than $10,000. Case Western Reserve University also holds equity in Copernicus Therapeutics, Inc., and has received royalties from Arizeke and from Copernicus.

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