An Overview of Cystic Fibrosis:

Genetics, Symptoms, Diagnosis, & Treatment

Nathaniel Peterson

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Robert Pietruszka

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Cystic fibrosis (CF) is a relatively rare yet life-threatening disease that affects approximately seventy thousand people worldwide, including thirty thousand Americans (Cystic Fibrosis Foundation-1, 2012). Occurrence of CF is highest among caucasians with an incidence of approximately 1 in 1000-4000 births depending on region (Shastri et al. 2008, Southern et al. 2007). Early recognition and treatment is vital to promoting a long and healthy lifespan. Left untreated, CF may be lethal and most affected individuals die in early adolescence, however, modern treatment options are extending life expectancy and improving quality of life for those affected (Cystic Fibrosis Foundation-1 2012). To better understand CF, several factors must be considered, including its genetic attributes, typical symptoms, the process of diagnosis, and available treatment options.

CF is caused by a mutated autosomal recessive allele (Griesenbach and Boyd 2005) that corresponds to the cystic fibrosis transmembrane conductance regulator (CFTR) gene located on chromosome seven (Shastri et al. 2008). Over seventeen hundred unique CFTR allele mutations are recognized (Lay-Son et al. 2011). Among them, type deltaF508 occurs in approximately 66% of CF patients and is characterized by a deletion of a codon—located at position 508 on the chromosome—used to create the amino acid phenylalanine (Sinaasappel et al. 2002). The CFTR gene codes for the production of a protein channel required to regulate chloride ion concentration between the plasma membranes of associated cells (Griesenbach and Boyd 2005). This protein is commonly expressed in the epithelial cells that line the airways of lungs and various passages of the pancreas, liver, intestines, reproductive organs, and skin (Starr et al. 2009). Faulty CFTR alleles are responsible for creating defective variations of this protein or terminating its production and as a result, CF symptoms occur (Laurie and Fundukian 2011).

The most universally characteristic and life-threatening symptom of CF is lung airway obstruction caused by progressive buildup of dehydrated mucus (Bilton and Hurt 2012). In healthy lung tissue, chloride transport proteins move chloride ions out of epithelial cells to create a concentration gradient across the plasma membrane that water molecules follow via osmosis (Zemanick et al. 2010). As water molecules exit the cells, a thin extracellular fluid layer forms which supports tissue immunity and

functions as an epithelial lubricant (Bilton and Hurt 2012). In cystic fibrosis-afflicted lung tissue, the chloride transport proteins are rendered ineffective and as a result, chloride ions stagnate inside the cells failing to produce the concentration gradient necessary for water movement (Zemanick et al. 2010). Dry sticky mucus then persists on the surface of epithelial cells; this obstruction and irritation inevitably results in inflammation and bacterial infections of the lung tissue (Konstan et al. 2011).

CF is an autosomal recessive trait, meaning it is passed down by both parents and is not dependent on sex for its expression (Starr et al. 2009). Individuals that have inherited only one copy of the allele do not express the trait, but are carriers for it (Starr et al. 2009). This means that affected individuals possess a homozygous genotype while carriers have a heterozygous genotype (Starr et al. 2009). Heterozygous parents therefore present to each of their children a 25% chance of expressing the trait, a 50% chance of being carriers for it, and a 25% chance that they will neither express the trait nor be carriers for it (Starr et al. 2009).

Coping with CF can be difficult for both patients and loved ones due to the immense amount of suffering it incurs. An important aspect of reducing such suffering is early diagnosis (Sims et al. 2005). Today, the United States has newborn screening (NBS) programs operating in all fifty states designed to detect CF (among many other common health abnormalities) using a variety of methods (Groose et al. 2010). NBS involves acquiring blood samples from infants within the first several days following birth (Cystic Fibrosis Foundation-2 2012). Infants who test positive for CF during a screening undergo more thorough testing to verify results, most commonly in the form of a sweat test (Southern et al. 2007).

Health care providers may perform a sweat test using one or more techniques such as measuring sweat chloride levels and conductivity (Southern et al. 2007). This is frequently done using quantitative pilocarpine iontopheresis and is considered to be among the most reliable forms of testing (Beauchamp et al. 2005). Ninety-eight percent of CF patients' sweat chloride levels have been shown to be 3-5 times higher than controls in some studies and if test results indicate such abnormally high chloride levels in sweat, CF diagnosis is likely (Leonard et al. 2008). Borderline levels, however, may necessitate second

tier evaluations such as gene analysis to arrive at reliable conclusions (Mayell et al. 2007).

The few individuals who receive a positive diagnosis for CF are challenged with the task of effectively treating this complex disease. There are, however, a number of physical therapy and drug treatment options available that show a limited degree of success. Postural drainage and percussion (PDP) is a conventional physical therapy technique performed on CF patients and is simple enough to be learned and performed by non-healthcare professionals (Cystic Fibrosis Foundation-3 2012). PDP requires the patient to sit or lay down in a variety of different positions to receive manual percussion and vibration around the chest (Cystic Fibrosis Foundation-3 2012). Combined with breathing exercises by the patient, PDP makes coughing more productive and could make subsequent inhaled medication treatments more efficient (Cystic Fibrosis Foundation-3 2012).

Mannitol is an inert sweet-tasting substance found in plants and is frequently used in pharmaceuticals (Bilton and Hurt 2012). Inhaled medications such as dry powder mannitol (IDPM) have shown to improve lung function in CF patients versus placebo in a recent trial and resulted in minimal side-effects (Bilton and Hurt 2012). Research shows that its efficacy is in its ability to reduce the viscosity of respiratory mucus by interfering with their hydrogen bonds, a feature that could help reduce the appearance of infection (Bilton and Hurt 2012). Other comparative treatments such as inhaled corticosteroids (ICS) may help to improve lung function and reduce bronchial inflammation (Ren et al. 2008). Other similar studies on the treatment, however, have shown inconclusive results (Ren et al. 2008).

Pseudomonas aeruginosa is a bacterium, among others, commonly associated with CF respiratory tract infections and is a primary contributor to the progressive decline in lung function (Ren et al. 2008). *P. aeruginosa* is particularly resilient and tends to produce large amounts of biofilm and alginate bi-products in the lower respiratory tract (Hansen et al. 2005). The biofilm produced by the invading bacteria serves as a defense from immune responses and certain medications (Hansen et al. 2005). CF patients afflicted with *P. aeruginosa* respiratory infection, after receiving inhaler-delivered tobramycin powder in one trial, however, displayed a significant increase in forced expiratory volume with a simultaneously

reduced concentration of *P. aeruginosa* in sputum at all treatment intervals (Konstan 2011). Azitromycin antibiotic treatment is another effective remedy for *P. aeruginosa* infection in CF patients that has been demonstrated to improve lung function (Hansen et al. 2005). The efficacy of these medications is significant because some research suggests that as much as 95% of CF patient deaths in the past have been due to respiratory infections associated with *P. aeruginosa* bacteria (Hansen et al. 2005).

CF-related pancreatic insufficiency tends to result in delayed growth and wasting of the human body from malnutrition (Wilson and Pencharz 1998). Body weight correlates directly to CF patient health and studies suggest that high calorie diets rich in fat and protein may serve to improve CF symptoms by facilitating weight gain (Sinaasappel et al. 2002). Research shows that, among other factors, malnutrition is associated with fat malabsorption in the intestines (Sinaasappel et al. 2002). Fat absorption is five to ten percent less than healthy controls and studies indicate that this is mainly caused by reduced secretions of pancreatic lipase, an enzyme involved in fat digestion (Wouthuyzen-Bakker et al. 2011). Infants and newborns have been shown to benefit from pancreatic enzyme replacement therapy in the form of Creon, a lipase supplement (Munck et al. 2009). Pancreaze, a lipase, protease and amylase supplement, has also shown positive results in clinical trials (Trapnell et al. 2011). Patients undergoing enteral feeding may similarly benefit from growth-hormone supplementation as a means of stimulating growth and weight-gain (Hardin et al. 2004).

Perhaps the most promising treatment for CF patients comes in the form of a new drug developed by Vertex Pharmaceuticals called "Kalydeco" (US Food & Drug Administration 2012). In January of 2012, the FDA made a press release regarding their approval of Kalydeco, a drug that reportedly helps to restore function to the defective protein associated with CF in the 4% of the patient population that have the G551D mutation (US Food & Drug Administration 2012). Prior to its approval, the drug was involved in forty-eight weeks of testing with 213 patients (US Food & Drug Administration, 2012). According to the press release, patients using Kalydeco experienced "significant and sustained improvement in lung function" compared to placebo treatment (US Food & Drug Administration 2012). Two other Vertex

drugs are currently being tested and could potentially treat CF patients with the deltaF508 mutation if testing produces positive results (Cystic Fibrosis Foundation-4 2012). This could be the medical science breakthrough that thousands of individuals have been waiting for.

Cystic fibrosis exerts a cumulative impact on the human body and spirit that is tragic and heart-breaking. Its detrimental effects on men, women and children are both impartial and unforgiving. Cystic fibrosis disrupts function in many parts of the body, but its most devastating tendency is a certain and progressive deterioration of one's ability to breathe, a vital life activity that many of us take for granted. Without a reliable cure, patients of cystic fibrosis are resigned to coping with its merciless symptoms through the use of medication and physical therapy. Yet today, cystic fibrosis patients are living longer and healthier lives (Cystic Fibrosis Foundation-1, 2012). Creative men and women are continuously unraveling the mysteries that tie cystic fibrosis to the human body. Thanks to their diligent efforts in medical science, patients may one day soon experience a breath of fresh air.

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