Module 1: Introduction to the Disease

Cystic Fibrosis (CF) is one of the most common lethal genetic disorders in America, affecting approximately 1 in 3,200 Caucasian newborns, and 1 in 3,900 of all newborns in America. CF leads to a build-up of thick mucus in the lungs and intestines. The illness causes breathing problems, malnutrition and chronic respiratory infections. Although life expectancy for people with CF has increased, the median life expectancy is still only in the mid 30s (Cystic Fibrosis Foundation (CFF), 2002). CF is an autosomal recessive disease most prevalent in Ashkenazi Jews and Caucasians of European decent, where approximately 1 in 29 people carry the altered gene. The prevalence is diminished in other major ethnic groups: 1 in 46 for Hispanic Americans, 1 in 62 for African Americans and 1 in 90 for Asian Americans (Baskin et al., 2002).

The "classic" type of cystic fibrosis occurs when a person inherits two copies of a faulty gene—one from each parent—for a protein called CFTR. This protein transports chloride ions in and out of cells and is especially important in the lungs. Absence of working CFTR leads to the abnormal secretions that occur in CF. In the "nonclassic" form of CF, individuals have at least one abnormal copy of the CFTR gene, but unlike in classic CF, the CFTR protein retains some function. Though many of the symptoms are similar, patients with nonclassic CF are less likely to suffer from malnutrition (Knowles and Durie, 2002).

CF affects nearly all the exocrine glands, which are the glands that secrete fluids into a duct. The secretions are abnormal in different ways and affect gland function. In the digestive-enzyme secreting glands of the pancreas and intestine, the secretions are thick or solid and may block the gland completely. The mucus-producing glands of the lungs produce abnormal secretions that clog the airways and allow bacteria to multiply. The sweat glands, parotid glands, and small salivary glands secrete fluids containing more salt than normal (Cysticfibrosis.com, 2002). CF is also characterized by persistent Pseudomonas aeruginosa colonization of the conducting airways in the lungs leading to the migration of inflammatory cells, including polymorphonuclear leukocytes (PMNs), into the airways of CF patients. PMNs release a potent chemokinetic and chemoattractant, leukotriene B, during an inflammatory response, resulting in the further migration of inflammatory cells (Berger, 2002). This inflammatory response damages epithelial cells of the lungs.

CF has a variety of symptoms affecting respiration, digestion, and secretory glands. The most common are: very salty-tasting skin, frequent infections of the lungs and sinuses, chronic coughing and wheezing, excessive appetite but poor weight gain, pancreatic insufficiency due to blockage of ducts that carry digestive enzymes, and vitamin deficiency due to lowered absorption of nutrients through the intestinal walls (Plourde, 2004). People with CF also often have impaired reproductive function.

The severity of symptoms in cystic fibrosis patients varies greatly between individuals, and is usually related to the degree of the patient’s respiratory problems. The prognosis for CF patients has improved steadily in the past 25 years, largely due to treatments that prevent infection and deterioration of the lungs (Merck, 2004). In 1969, half of CF patients died by the age of 14 (Cystic Fibrosis Services, 2002); today the median life expectancy is 33 (Merck, 2004). The treatment of CF depends upon the stage of the disease and which organs are involved.
Therapy includes prevention and treatment of lung problems, good nutrition, physical activity, and psychological and social support. Excluding access to medical treatment, the environment has little effect on the severity of the disorder. There is no cure for CF at this time, however, gene therapy holds great promise for treating this disease.

Cystic Fibrosis is caused by defects in the CFTR gene, or Cystic Fibrosis Transmembrane Conductance Regulator. The gene is located on the long arm of chromosome 7, band 31, subband 2 (locus 7q31.2). CFTR encodes a protein that normally resides in the membranes of cells and is involved in the transport of chloride ions into and out of cells. Lack of functional CFTR protein causes the lungs and pancreas to secrete the thick mucus, blocking passageways and causing respiratory and digestive problems. There are hundreds of known mutant alleles of the CFTR gene, but 70% of all people with Cystic Fibrosis carry the same mutation--a deletion of three base pairs within the coding region of CFTR that leads to the deletion of a single amino acid, phenylalanine, at position 508 (Kerem et al., 1989). Twelve other mutations account for 15% of cases, and hundreds of other mutations account for the remaining 15% of cases. The majority of CFTR mutations are inherited from unaffected carrier parents, rather than being new mutations.

Cystic fibrosis was first described and named by Dorothy H. Anderson in 1938. Dr. Anderson performed autopsies on infants and children with similar symptoms, reported comprehensive description of the symptoms of the disease, and gave the disease its name “cystic fibrosis of the pancreas” (Welsh and Smith, 1995). Since the defective CF gene was discovered in 1989 (Riordan et al., 1989), the pace of CF research has greatly accelerated. In 1990, scientists successfully made copies of the normal gene, and added them to CF cells in laboratory dishes, which corrected the defective cells. The next major step was achieved in early 1993 when the first experimental gene therapy treatment was given to a patient with CF. Researchers modified a common cold virus to act as a delivery vehicle - carrying the genes to the CF cells in the airways. Several studies are underway to test new gene delivery methods, such as fat capsules (liposomes) and synthetic vectors (CFF, 2004).

Considering that cystic fibrosis was lethal until very recently, it is surprisingly common in Caucasians (1/29 are carriers). Furthermore, the high frequency of a single mutation (deletion of phenylalanine 508), suggests that the allele is actively maintained in the population. One theory is that the mutated CF gene may be advantageous to the heterozygote by making them more resistant to certain pathogens. For example, Salmonella typhi, which causes typhoid fever, uses CFTR for entry into epithelial cells. Heterozygous delta-F508 Cftr mice internalized 86% fewer S. typhi than did wildtype mice (Pier et al, 1998). Cholera and pathogens that cause chloride ion secreting diarrheas also use CFTR as a gate into the cells. However, diarrhea-causing pathogens are found all over the world. So why were CFTR mutations only preserved in N. Europe? A possible explanation is that mutant alleles lead to chronic excessive salt loss, potentially a major disadvantage in hot climates (Quinton, 1994).

Numerous advocacy groups exist for cystic fibrosis. The Cystic Fibrosis Foundation supports CF research to cure and control cystic fibrosis and to improve the quality of life for those with the disease. The CF Foundation funds medical research and care programs for patients with CF.
Works Cited


