Lesson S14: PreAnesthetic Assessment of the Patient with Cystic Fibrosis – Part 1

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TIME TO COMPLETE ACTIVITY: 2 hours
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TARGET AUDIENCE: Anesthesiologists

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Needs statement
Approximately 30,000 Americans are affected by cystic fibrosis (CF). Although it is mainly a disease of the young, improvements in diagnosis and treatment have increased prevalence in older adults. Research is focused on gene manipulation and gene therapy. Knowledge of the pathophysiology of the disease and methods of early diagnosis enables physicians to anticipate problems and offer system-specific treatments.

This is a two part activity. Part 1 is presented here and will cover the historical significance, genetic application, and clinical manifestations of cystic fibrosis. Part 2 will present a discussion of diagnostic criteria, appropriate testing and perioperative management.

Learning Objectives
At the end of this activity, the participant should be able to:

1. Appreciate the historical background of cystic fibrosis
2. Cite the incidence of the disease in different populations
3. Explain the function of cystic fibrosis transmembrane conductance regulator (CFTR) protein
4. Outline the pattern of inheritance for CF
5. Identify common pathogens of pulmonary infection in CF
6. List the organ systems most usually affected
7. Tabulate the signs and symptoms of CF
8. Describe the pathology commonly seen in CF
9. Identify endocrine anomalies associated with CF
10. Differentiate between life expectancy rates now as compared to 20 years ago

**Case History**

A 15 year old girl presented to the emergency room with severe abdominal pain of 36 hours duration. Her medical history reveals a diagnosis of cystic fibrosis made shortly after birth, and frequent respiratory infections treated with multiple courses of antibiotics. She was also diabetic. A CT scan of her abdomen revealed a probable intussusception and she was scheduled for laparotomy.

**Introduction**

Cystic fibrosis is a monogenic, autosomal recessive disorder associated with multi-system organ dysfunction. Infants born with cystic fibrosis usually reach adulthood, making surgical procedures performed in this patient group more common. CF is a heterogeneous disorder characterized by widespread dysfunction of exocrine glands involving multiple organs causing a diverse range of pathologic and clinical problems. The defective gene in CF is expressed as altered body secretions such as saliva, sweat, digestive and pulmonary fluids. The normally thin, lubricating consistency is lost and secretions become thick and sticky causing plugged up tubes, ducts and passageways, especially in the pancreas and lungs. The most serious consequences of CF are lung disease and respiratory failure, typically affecting children and young adults. It remains the most common lethal hereditary disorder in the Caucasian population, and in the United States, it is the major cause of chronic debilitating pulmonary disease and pancreatic exocrine deficiency during the first three decades of life.¹⁻²

The clinical manifestations of CF include obstructive pulmonary disease, pancreatic insufficiency, abnormally high sweat electrolyte concentrations, nasal polyps, infertility, gastrointestinal obstruction and pansinusitis. In the late stages of the disease, patients may require lung, pancreas and liver transplantation.

Genetic testing affords early detection of the disease. Combined with the availability of reliable treatments, the life expectancy for those afflicted with CF has increased from teen years to 30s, with a corresponding improvement in physical comfort and quality of life.

Each year, approximately 3,200 Caucasian babies are born in the United States with CF. The disease is much less common among children of African and Asian descent. Two-thirds of infants born with CF are diagnosed in the first year of life. The prevalence of CF among adults and children in the United States is about 30,000. There is no cure and most research is directed at gene therapy to correct lung problems associated with CF.³
Historical Background

The earliest descriptions of infants and children with steatorrhea, pancreatic insufficiency, and meconium ileus (indicative of CF) are found in literature from the mid-17th century. European folklore of the 1700s and 1800s references early death among infants with salty skin. For example, literature from Germany and Switzerland states "Woe is the child who tastes salty from a kiss on the brow, for he is cursed, and soon must die". In the 19th century, Carl von Rokitansky described a case of fetal death with meconium peritonitis, a complication of meconium ileus later found to be associated with cystic fibrosis. Meconium ileus was first described in 1905 by Karl Landsteiner. In 1936, Guido Fanconi published a paper describing a connection between celiac disease, cystic fibrosis of the pancreas, and bronchiectasis.

In 1938, Dorothy Hansine Andersen published "Cystic Fibrosis of the Pancreas and its Relation to Celiac Disease: a Clinical and Pathological Study," in the American Journal of Diseases of Children. Andersen was the first to correlate cystic fibrosis of the pancreas with the lung and intestinal disease prominent in CF. She hypothesized that CF was a recessive disease and she was the first to use pancreatic enzyme replacement to treat affected children. She later proposed an autosomal-recessive pattern of inheritance. The generalized dysfunction of exocrine glands and the inability to clear secretions was suggested as a pathogenic mechanism of cystic fibrosis in 1945 by Farber. He introduced the term “mucoviscidosis,” which was used in medical literature for many years to describe cystic fibrosis.

In 1952, Paul di Sant' Agnese discovered abnormalities in sweat electrolytes. The pilocarpine iontophoresis sweat test was first described by Gibson and Cooke in 1959 following the validation of excessive salt loss in the sweat of children.

In 1988, the first mutation for CF -- ΔF508 -- was identified on the seventh chromosome by Francis Collins, Lap-Chee Tsui and John R. Riordan. Subsequent research has found over 1400 different genetic mutations that cause CF. In 1989, Lap-Chee Tsui and a team of researchers discovered the gene responsible for CF, at the Hospital for Sick Children in Toronto. Classical genetic techniques were unable to pinpoint the small mutations on the cystic fibrosis transmembrane conductance regulator (CFTR) gene. Protein markers and gene-linkage studies were used to map the mutation to chromosome. Chromosome-walking and -jumping techniques were then used to identify and sequence the gene. Cystic fibrosis represents the first genetic disorder elucidated strictly by the process of reverse genetics.

Research efforts in the mid-1980s focused on abnormalities in the mechanism of electrolyte movement in the cystic fibrosis epithelium. Studies showed that the attenuated chloride transport in the sweat ducts and respiratory epithelium was the basic physiologic defect of the disease. This altered movement of sodium chloride creates thick, sticky secretions in the respiratory, digestive and reproductive systems and increased salt in sweat.

The CFTR gene was first identified and cloned in 1989. Trials of gene therapy for cystic fibrosis using adenoviruses continue in several centers in the United States.
Genetic Implications

Incidence and Prevalence

CF is a genetic disorder found in many ethnic and racial groups. The prevalence of the disease in the United States varies with the ethnicity, and is highest in individuals of northern and central European descent. Cystic fibrosis occurs with an incidence of 1 in 2500 live births in Caucasians in North America, Australia, and northern and central Europe; 1 in 17,000 live births in African-Americans; and 1 in 90,000 live births among Asians in Hawaii. The disease appears to occur with a similar prevalence worldwide. CF is most common among Caucasians and Ashkenazi Jews; and 1 in 25 people of European descent carry one gene for CF.

Life expectancy can depend largely on access to health care. In 1959, the median age of survival of children with CF was 6 months. In the United States, the life expectancy is reported to be 37.4 years for infants afflicted with CF born in 2008 (based on data complied by the Cystic Fibrosis Foundation). In Canada, the life expectancy is reported to be 47.7 years.

Pattern of Inheritance

Cystic fibrosis is an autosomal-recessive trait that affects males and females with equal frequency. It is estimated that among Caucasians, 4% (1 in 25) to 5% (1 in 20) are heterozygous carriers of the defective gene. The risk that a child will inherit cystic fibrosis depends on the genotypes of both parents and ranges from 1 in 4 for known carriers to 1 in 2500 for parents with no family history of cystic fibrosis. For parents with a child with CF, there is a 1 in 4 chance of giving birth to another child with CF. In such families, two-thirds of unaffected siblings will be carriers. Children must inherit two copies of the recessive gene, one from each parent, in order to have the disease. If children inherit only one copy, they do not develop CF, but they may be carriers and possibly pass the gene to their children. Two carrier parents have a 25 percent risk of conceiving a child with CF, a 50 percent risk of conceiving a child who is carrier of the defective CF gene, and a 25 percent chance of conceiving a child that will not be a carrier or have the disease. People who carry the CF gene (heterozygotes) are healthy and have no symptoms of disease.

The high frequency of cystic fibrosis gene in Caucasian populations has been the subject of controversy for many years. Individuals affected with lethal diseases, such as CF, usually die without producing children, which usually leads to the eventual disappearance of the defective trait over time. The high incidence cannot be explained by a spontaneous, recurrent mutation since such a rate is too low to maintain the current incidence of cystic fibrosis carriers. The heterozygotic advantage has been proposed as one possible explanation of the persistent presence of the cystic fibrosis gene in the population. Increased resistance to tuberculosis and syphilis infections and increased fertility in male heterozygotes all have been postulated, but none has been proven. Cystic fibrosis heterozygote resistance to cholera toxin in the mouse model has been documented. This observation supports the hypothesis that a human cystic fibrosis heterozygote may possess a selective advantage in surviving the potentially fatal effects of secretory diarrhea and possibly provides an explanation for the high incidence of cystic fibrosis carriers.
CFTR - the Cystic Fibrosis Gene

The first described and the most common mutation of the CFTR is ΔF508 -- a deletion (Δ) of three nucleotides that results in the loss of phenylalanine (F) at the 508th (508) position on the protein.\textsuperscript{13} The ΔF508 mutation accounts for 50%–80% of all cystic fibrosis alleles.\textsuperscript{28} Its frequency varies among ethnic groups. It is found in 70%–80% of northern Europeans and white and Hispanic Americans with cystic fibrosis, in 40%–50% of southern Europeans, in 37% of African-Americans, and in 30% of Ashkenazi Jews in North America.\textsuperscript{20} Approximately 50% of all cystic fibrosis patients in North America are homozygous for ΔF508 alleles.\textsuperscript{22}

The CFTR gene consists of approximately 230–250 Kb of DNA and contains 27 coding exons.\textsuperscript{12–14} The gene is expressed in epithelial cells and encodes the CFTR protein. Normal individuals carry unaltered forms of the gene, whereas cystic fibrosis patients and heterozygote carriers bear the mutant copies.

The CFTR gene, found at the q31.2 locus of chromosome 7, is 230,000 base pairs long. The gene creates a CFTR protein that is a single polypeptide chain of 168kDa containing 1480 amino acids.\textsuperscript{28,31} Structurally, CFTR is a type of gene known as an ABC gene. The product of the CFTR is a halide anion channel important in creating sweat, digestive juices and mucus. This protein possesses two ATP-hydrolyzing domains which allow the protein to use energy in the form of ATP. It also contains two domains each comprised of 6 alpha helices which allow the protein to cross the cell membrane. A regulatory binding site on the protein allows activation by phosphorylation, mainly by cAMP-dependent protein kinase. The carboxyl terminal of the protein is anchored to the cytoskeleton by a PDZ domain interaction.

The CFTR protein consists of two symmetrical halves, each containing a hydrophobic membrane spanning domain (MSD) and a hydrophilic cytoplasmic nucleotide binding fold (NBF).\textsuperscript{27–30} These two halves are joined by a large, highly charged cytoplasmic domain, named the regulatory, or R, domain, that has a number of phosphorylation sites for protein kinases A and C.\textsuperscript{19,27–30} Each MSD has six regions that span the membrane and contribute to the formation of the chloride channel, whereas each NBF serves as a location for the adenosine triphosphate (ATP) binding and cleavage.\textsuperscript{19,30,31} The NBF closest to the N-terminus is the locus of the most common cystic fibrosis mutation (i.e., ΔF508).\textsuperscript{31} The amino acid sequence and the protein structure of CFTR show a striking resemblance to a superfamily of proteins that are found in various species and are involved in active transport of molecules across cell membranes.\textsuperscript{19,28,30}

The CFTR protein has been localized to the apical membrane surfaces of specialized transporting epithelial cells in the pancreas, sweat glands, lungs, and intestine.\textsuperscript{19,31} It appears to function as a low-conductance chloride channel that is regulated by cAMP-dependent phosphorylation, although it may have other functions.\textsuperscript{27–31} The absence of the fully processed and functional CFTR protein in the apical membrane or the presence of its nonfunctional form results in abnormal chloride ion transport, which is the underlying defect in the cystic fibrosis epithelium.

There is increasing evidence that genetic modifiers besides CFTR modulate the frequency and severity of the disease. One example is mannan-binding lectin, which affects innate immunity by facilitating phagocytosis of microorganisms. Polymorphisms in one or both mannan-binding lectin alleles that result in lower circulating levels of the protein are associated with a threefold higher risk of end-stage lung disease, as well as an increased burden of chronic bacterial infections.
At present, more than 1400 mutations have been recognized in the CFTR gene. These consist of missing, nonsense, frame-shift, in-frame deletion, and splicing mutations. The location of these defects is relatively symmetrical, with the majority occurring in exons 4, 7, 11, 13, 17b, and 19. The mutations have been divided into four classes relative to the final protein product. Class I mutations produce completely defective proteins; class II mutations generate premature degradation of partially processed protein; class III mutations lead to impaired regulation of the fully processed protein; and class IV corrupts the function of the CFTR. Class I and II mutations eliminate CFTR in the affected cell, whereas class III and IV mutations produce nonfunctional CFTR protein. The ΔF508 mutation is a class II defect.

There seems to be some correlation between the type of mutation and the phenotype of the disease produced. The ΔF508 and other class I and II mutations are associated with classic and severe cystic fibrosis with pancreatic insufficiency. Class III and IV mutations are associated with less severe disease. Although genetic screening for most common mutations allows detection of nearly 90% of cystic fibrosis carriers, the large number of other mutations and the inability to detect all cystic fibrosis mutations limits the prospect of general population screening. At present, DNA screening technologies are used for those with a positive family history.

**Pathophysiology**

Fundamental pathophysiologic findings in cystic fibrosis include abnormal ion concentrations in the secretions from serous glands, especially increased sodium and chloride content in sweat; decreased water content and increased viscosity of secretions from mucus glands, with failure to clear secretions, obstruction, and ultimate glandular destruction; and a unique propensity for chronic respiratory tract colonization and infection by specific groups of bacteria. The first two observations may be explained by abnormal cAMP-regulated chloride channel activity in cystic fibrosis epithelium. Infections are probably secondary developments.

**Ion Transport**

All affected cystic fibrosis epithelia share a common biophysical characteristic: the transepithelial electrical potential difference is higher than that of normal epithelia. The transepithelium electrical potential difference is a reflection of both the rate of active ion transport and the resistance to ion flow across the epithelium. It is well established that the apical membranes of various cystic fibrosis epithelia are impermeable to the chloride ion. In their native state, affected epithelia perform different functions in terms of electrolyte and water transport. The defect of chloride impermeability produces diverse effects in diseased epithelia.

The epithelia of sweat ducts and other serous ducts are normally salt-absorbing. In cystic fibrosis, epithelial cell membranes of sweat ducts are impermeable to chloride and thus excessive amounts of salt are lost in the sweat. The epithelium of the airway normally secretes chloride and, secondarily, sodium and water onto the epithelial surface. This physiologic mechanism maintains hydration of the airway secretions. The cystic fibrosis airway epithelium limits chloride transfer into the airway lumen because of underlying chloride impermeability. Reabsorption of sodium from the airway surface into the cell is abnormally increased, leading to decreased salt and water content in airway secretions. These ion transport abnormalities create viscous, dehydrated airway secretions that are the hallmark of the clinical picture of cystic fibrosis.
The defective chloride transport in cystic fibrosis pancreatic ductal epithelium leads to inadequate secretion of sodium bicarbonate and water into the pancreatic duct, retention of pancreatic enzymes, and destruction of the organ tissue. Similarly, failure to secrete chloride and water causes obstructive problems resulting from production of sticky, dehydrated material in the intestines, liver, gallbladder, and genitourinary tract.

**Infection**

Chronic infection in individuals with cystic fibrosis primarily affects the respiratory tract. At birth, the lung tissue of patients with cystic fibrosis has a normal histologic appearance. During the first two years of life, an endobronchial colonization process begins and initially involves the mucociliary layer of the peripheral airways, with minimal parenchymal involvement. Subsequently, persistent colonization and associated peribronchial inflammation results in bronchiectasis and increased parenchymal involvement, with micro abscess formation and focal hemorrhagic pneumonia.

The most common pathogen isolated from the airways of patients with cystic fibrosis is *Pseudomonas aeruginosa*. Studies report that colonization can exceed rates of 70%. A progressive deterioration of pulmonary status usually follows the initial colonization. The initial colonizing organism in the airway is typically *Staphylococcus aureus* which rarely produces fulminant disease and is later replaced by *P. aeruginosa*. Colonization with *Pseudomonas cepacia* is being reported with increasing frequency. Other organisms less frequently associated with cystic fibrosis include *Haemophilus influenzae*, *Escherichia coli*, *Klebsiella species*, *Proteus species*, *Serratia species*, *Actinobacillus species*, *P. fluorescens*, and *P. multiphilia*. These pathogens are usually transient and commonly supplanted by *P. aeruginosa*.

This unique pattern of airway colonization with *P. aeruginosa* and *S. aureus* is incompletely understood. One proposed explanation is that the abnormal structure of mucous glycoproteins favors the adherence of the specific bacteria to the affected respiratory epithelial surface. Defective immunity and possible nutritional deficits also may be contributory factors in the development and persistence of chronic respiratory tract infections.

**Clinical Manifestations**

Clinical manifestations of cystic fibrosis are most apparent in the respiratory tract, gastrointestinal tract, and genitourinary system. Because of multi-organ involvement, cystic fibrosis mimics a number of other clinical entities.

Patients diagnosed with CF during the intrapartum period or during early childhood typically present with respiratory tract symptoms such as persistent cough and/or refractory pulmonary infiltrates. Meconium ileus occurs in approximately 10% of patients within the first days of life, with subsequent steatorrhea and failure to thrive throughout infancy. The diagnosis of CF is not established until adolescence or young adulthood in nearly 10% of cases.

The severity of the disease can be reflected in the symptoms. For example, a child may have respiratory problems or digestive problems or both. Symptoms of CF also vary with age. Newborns often present with meconium ileus because of the inability to pass abnormally thick meconium in the
first two days of life. Other symptoms in newborns may include a failure to grow, steatorrhea and frequent respiratory infections.

Table 1 presents the signs and symptoms typical of CF in children and young adults.

**Respiratory Tract**

The most frequent complications of CF are chronic respiratory infections, including pneumonia, bronchitis and bronchiectasis. Thick mucus secretions block the airways and provide a favorable medium for bacterial growth. Antibiotics can decrease the frequency and severity of attacks, although bacterial colonization can persist.

Upper respiratory tract involvement is almost universal in cystic fibrosis. Hyperactive mucus-secreting glands that produce increased volumes of upper airway secretions, as well as edema and hypertrophy of the mucous membranes, lead to chronic nasal congestion and rhinorrhea. Radiographic evidence of opacification of all sinuses is common. Nasal polyps, multiple and bilateral, are found in 15% –20% although the incidence is highest during mid-childhood and they are rarely seen before age 5 years or after age 20. Polyps often require surgery, and recurrence is common.

Progressive bronchiectasis, secondary to obstruction of the small airways by thick secretions, occurs in most patients over 18 months. The pulmonary course is characterized by alternating periods of clinical stability and episodes of exacerbations triggered by acute infections. Frequent exacerbations result in a progressive loss of lung function and respiratory failure.

One of the earliest manifestations of cystic fibrosis lung disease is an intermittent, dry cough associated with acute respiratory tract infection. The cough can become a chronic condition that persists beyond the period of infection. With pulmonary exacerbations, the cough can become productive and paroxysmal with associated gagging, choking, and vomiting. It is frequently worse at night and in the morning. Sputum is characteristically viscous, purulent, and often greenish due to *P. aeruginosa* infection. Lung sounds are initially clear or diminished, but with exacerbations wheezing, rales, and rhonchi become prominent. There is significant hyperinflation of the lungs noted early in the course of the disease. Atelectasis, pneumothorax, and hemoptyisis are common complications in advanced stages. Pneumothorax occurs as a result of rupture of apical subpleural blebs and has an incidence of 2%–10%. Life-threatening massive hemoptyisis occurs from eroded bronchial arteries, and has a high recurrence rate and poor prognosis.

Other clinical features of pulmonary involvement include a barrel-chest deformity, use of accessory muscles for respiration, growth retardation, hypertrophic pulmonary osteoarthropathy, digital clubbing, decreased exercise tolerance; and in end-stage lung disease, pulmonary hypertension, cor pulmonale, and respiratory failure with cyanosis. In addition to the aforementioned bacterial infections (e.g. *P. aeruginosa*, *S. aureus*) up to 50% of cystic fibrosis patients have positive growth of *Aspergillus*.
Gastrointestinal Tract

Gastrointestinal symptoms are prominent in the diagnosis of cystic fibrosis in infants and young children. Meconium ileus presents as intestinal obstruction with abdominal distention, failure to pass stool, and vomiting within 48 hours of birth in an infant who appears otherwise well. Approximately 50% of cases of meconium ileus are complicated by volvulus, atresia, and/or meconium peritonitis. Infants with cystic fibrosis have an increased risk of distal intestinal obstruction later in life.

Meconium ileus equivalent or distal intestinal obstruction syndrome occurs in older children and young adults. It is characterized by right lower quadrant pain, a palpable cecal mass, and partial or complete intestinal obstruction by firm, putty-like material in the terminal ileum and/or right colon. This syndrome can sometimes resemble acute appendicitis. Another occasional cause of intestinal obstruction is intussusception. Rectal prolapse is found in approximately 20% of children with cystic fibrosis. Factors associated with rectal prolapse include increased intraabdominal pressure due to distended bowel and coughing, poor muscle tone, and loss of perirectal fat that normally supports the rectum.

Exocrine pancreatic dysfunction is present in 90% of patients. The deficiency of pancreatic enzymes manifests as fat and protein indigestion and results in production of frequent, pale, bulky, and foul-smelling stools. Untreated patients develop steatorrhea, azotorrhea, and growth failure. Chronic diarrhea leads to malnutrition and vitamin deficiency.

Pancreatic enzymes necessary for fat and protein digestion are obstructed by thick secretions and are unable to reach the intestines resulting in malabsorption of fat-soluble vitamins such as A, D, E and K. Vitamin A deficiency causes increased intracranial pressure with bulging fontanelles in infancy, xerophthalmia, and night blindness. Lack of vitamin D rarely manifests as rickets; more often, it is associated with secondary hyperparathyroidism, reduced bone mineral content, and delayed bone maturation. Vitamin E deficiency causes red blood cell destruction and neuroaxial dystrophy. Vitamin K deficiency can lead to severe bleeding as a result of hypoprothrombinemia and inadequate levels of clotting factors II, VII, IX, and X.

Endocrine pancreatic function is preserved in most patients with cystic fibrosis until the second or third decade of life, when frank diabetes mellitus (type 1 insulin dependent) may occur in a small percentage of patients (about 7%). Hepatobiliary disease manifests as focal biliary cirrhosis as the bile duct becomes occluded. It affects 2%–5% of patients and presents as hyperbilirubinemia, ascites, and peripheral edema or massive hematemesis caused by esophageal varices.

Genitourinary System

Delayed onset of puberty is common in both males and females with cystic fibrosis. Azoospermia and infertility are seen in 98% of adult males because of mechanical obstruction of sperm transport secondary to absence or atresia of the vas deferens. The incidence of abnormalities associated with testicular descent, such as inguinal hernia, hydrocele and undescended testicles, is increased. Female
fertility may be as low as 20%.\textsuperscript{37} Many women with cystic fibrosis are anovulatory because of chronic lung disease.\textsuperscript{37} Thick, viscous cervical mucus acts as a barrier to sperm penetration. When pregnancy does occur, 90\% produce a viable infant.\textsuperscript{36} Women with cystic fibrosis generally are able to breast-feed normally. In addition, use of oral contraceptives can sometimes aggravate certain symptoms of CF. Female patients with CF should be guided by a physician when making decisions about birth control.

Part 2 will present a discussion of diagnostic criteria, appropriate testing and perioperative management. It will be available in November, 2010.

Dr. Elizabeth A.M. Frost, who is the editor of this continuing medical education series, is clinical professor of anesthesiology at The Mount Sinai School of Medicine in New York City. She is the author of Clinical Anesthesia in Neurosurgery (Butterworth-Heinemann, Boston) and numerous articles. Dr. Frost is past president of the Anesthesia History Association and former editor of the journal of the New York State Society of Anesthesiologists, Sphere. She is also editor of the book series based on this CME program, Preanesthetic Assessment, Volumes 1 through 3 (Birkhäuser, Boston) and 4 through 6 (McMahon Publishing, New York City).
REFERENCES


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**Post-test**

1. The incidence of CF in the Caucasian population in North America is:
   a. Unknown
   b. One in 17,000 live births
   c. One in 2500 live births
   d. Notably higher in the State of Hawaii

2. In women of child-bearing years with CF:
   a. Fertility is normal
   b. Use of oral contraceptives may aggravate symptoms
   c. Breast feeding is not recommended
   d. Babies are at 75% risk of developing the disease

3. The CFTR protein:
   a. Is found mainly in the central nervous system
   b. Contains almost 1500 amino acids
   c. Consists of 2 polypeptide chains
   d. Functions as a high conductance chloride channel

4. The underlying defect in CF epithelium includes abnormal transport of:
   a. Potassium
   b. Glucose
   c. Sodium
   d. Chloride

5. The most common bacteria isolated from the airway of patients with CF is:
   a. *E. coli*
   b. Tuberculum bacillus
   c. *S. aureus*
   d. *P. aeruginosa*
6. Clinical manifestations of CF are least likely to be seen in the:
   a. Brain
   b. Nose
   c. Lungs
   d. Pancreas

7. Regarding inheritance of CF:
   a. A dominant pattern is frequently described
   b. An autosomal recessive pattern predominates
   c. All carriers manifest the disease
   d. Only females are carriers

8. CFTR, the cystic fibrosis gene, is:
   a. Is abnormal in patients with CF
   b. Is located on chromosome 26
   c. Is not present in normal individuals
   d. Rarely mutates

9. Cystic fibrosis:
   a. Was described in children in the 17th century
   b. Is a systemic, recessively inherited disease
   c. Is not curable
   d. All of the above

10. A major pathophysiologic finding in CF is:
    a. Increased sodium and chloride in sweat
    b. Increased water content of mucus
    c. Glandular hypertrophy
    d. Normal ion concentrations in serous glands