Cystic Fibrosis

What Is Cystic Fibrosis

Cystic fibrosis (CF) is a chronic, progressive, and frequently fatal genetic (inherited) disease of the body's mucus glands. CF primarily affects the respiratory and digestive systems in children and young adults. The sweat glands and the reproductive system are also usually involved. On the average, individuals with CF have a lifespan of approximately 30 years.

CF-like disease has been known for over two centuries. The name, cystic fibrosis of the pancreas, was first applied to the disease in 1938.

How Common Is CF?

According to the data collected by the Cystic Fibrosis Foundation, there are about 30,000 Americans, 3,000 Canadians, and 20,000 Europeans with CF. The disease occurs mostly in whites whose ancestors came from northern Europe, although it affects all races and ethnic groups. Accordingly, it is less common in African Americans, Native Americans, and Asian Americans. Approximately 2,500 babies are born with CF each year in the United States. Also, about 1 in every 20 Americans is an unaffected carrier of an abnormal "CF gene." These 12 million people are usually unaware that they are carriers.

What Are the Signs and Symptoms of CF?

CF does not follow the same pattern in all patients but affects different people in different ways and to varying degrees. However, the basic problem is the same—an abnormality in the glands, which produce or secrete sweat and mucus. Sweat cools the body; mucus lubricates the respiratory, digestive, and reproductive systems, and prevents tissues from drying out, protecting them from infection.

People with CF lose excessive amounts of salt when they sweat. This can upset the balance of minerals in the blood, which may cause abnormal heart rhythms. Going into shock is also a risk.

Mucus in CF patients is very thick and accumulates in the intestines and lungs. The result is malnutrition, poor growth, frequent respiratory infections, breathing difficulties, and eventually permanent lung damage. Lung disease is the usual cause of death in most patients.

CF can cause various other medical problems. These include sinusitis (inflammation of the nasal sinuses, which are cavities in the skull behind, above, and on both sides of the nose), nasal polyps (fleshy growths inside the nose), clubbing (rounding and enlargement of fingers and toes), pneumothorax (rupture of lung tissue and trap-

ping of air between the lung and the chest wall), hemoptysis (coughing of blood), cor pulmonale (enlargement of the right side of the heart), abdominal pain and discomfort, gassiness (too much gas in the intestine), and rectal prolapse (protrusion of the rectum through the anus). Liver disease, diabetes, inflammation of the pancreas, and gallstones also occur in some people with CF.

When Should You Suspect That a Child May Have CF?

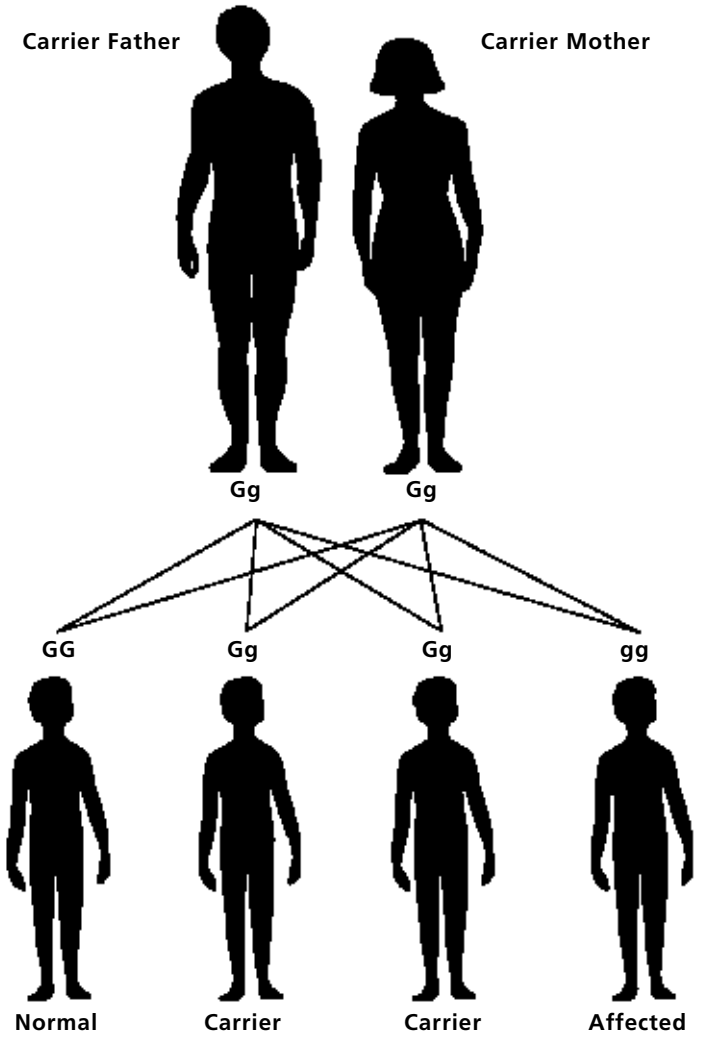
CF symptoms vary from child to child. A baby born with the CF genes usually has symptoms during its first year. Sometimes, however, signs of the disease may not show up until adolescence or even later. Infants or young children should be tested for CF if they have persistent diarrhea, bulky foul-smelling and greasy stools, frequent wheezing or pneumonia, a chronic cough with thick mucus, salty-tasting skin, or poor growth. CF should be suspected in babies born with an intestinal blockage called meconium ileus.

How Is CF Diagnosed?

The most common test for CF is called the sweat test. It measures the amount of salt (sodium chloride) in the sweat. In this test, an area of the skin (usually the forearm) is made to sweat by using a chemical called pilocarpine and applying a mild electric current. To collect the sweat, the area is covered with a gauze pad or filter paper and wrapped in plastic. After 30 to 40 minutes, the plastic is removed, and the sweat collected in the pad or paper is analyzed. Higher than normal amounts of sodium and

CYSTIC FIBROSIS GENE

AUTOSOMAL RECESSIVE INHERITANCE



The presence of two mutant genes (g) is needed for CF to appear. Each parent carries one defective gene (g) and one normal gene (G). The single normal gene is sufficient for normal function of the mucus glands, and the parents are therefore CF-free. Each child has a 25 percent risk of inheriting two defective genes and getting CF, a 25 percent chance of inheriting two normal genes, and a 50 percent chance of being an unaffected carrier like the parents.

chloride suggest that the person has cystic fibrosis.

The sweat test may not work well in newborns because they do not produce enough sweat. In that case, another type of test, such as the immunoreactive trypsinogen test (IRT), may be used. In the IRT test, blood drawn 2 to 3 days after birth is analyzed for a specific protein called trypsinogen. Positive IRT tests must be confirmed by sweat and other tests.

Also, a small percentage of people with CF have normal sweat chloride levels. They can only be diagnosed by chemical tests for the presence of the mutated gene. Some of the other tests that can assist in the diagnosis of CF are chest x-rays, lung function tests, and sputum (phlegm) cultures. Stool examinations can help identify the digestive abnormalities that are typical of CF.

What Makes CF a Genetic Disease?

Genes are the basic units of heredity. They are located on structures within the cell nucleus called chromosomes. The function of most genes is to instruct the cells to make particular proteins, most of which have important life-sustaining roles.

Every human being has 46 chromosomes, 23 inherited from each parent. Because each of the 23 pairs of chromosomes contains a complete set of genes, every individual has two sets (one from each parent) of genes for each function. In some individuals, the basic building blocks of a gene (called base pairs) are altered (mutated). A mutation can cause the body to make a defective protein or no protein at all. The result is a loss of some essential biological function and that leads to disease. Children may inherit altered genes from one or both parents.

Diseases such as CF that are caused by inherited genes are called genetic diseases. In CF, each parent carries one abnormal CF gene and one normal CF gene but shows no evidence of the disease because the normal CF gene dominates or "recesses" the abnormal CF gene. To have CF, a child must inherit two abnormal genes—one from each parent. The recessive CF gene can occur in both boys and girls because it is located on non-sex-linked chromosomes called autosomal chromosomes. CF is therefore called an autosomal recessive genetic disease.

The inheritance patterns for the CF gene are shown in the accompanying diagram. Each child, whether male or female, has a 25 percent risk of inheriting a defective gene from each parent and of having CF. A child born to two CF patients (an unlikely event) would be at a 100 percent risk of developing CF.

How Is CF Treated?

Since CF is a genetic disease, the only way to prevent or cure it would be with gene therapy at an early age. Ideally, gene therapy could repair or replace the defective gene. Another option for treatment would be to give a person with CF the active form of the protein product that is scarce or missing.

At present, neither gene therapy nor any other kind of treatment exists for the basic causes of CF, although several drug-based approaches are being investigated. In the meantime, the best that doctors can do is to ease the symptoms of CF or slow the progress of the disease so the patient's quality of life is improved. This is achieved by antibiotic therapy combined with treatments to clear the thick mucus from the lungs. The therapy is tailored to the needs of each patient. For patients whose disease is very advanced, lung transplantation may be an option.

CF was once always fatal in childhood. Better treatment methods developed over the past 20 years have increased the average lifespan of CF patients to nearly 30 years. These treatment approaches are detailed more fully below:

- Management of lung problems

A major focus of CF treatment is the obstructed breathing that causes frequent lung infections. Physical therapy, exercise, and medications are used to reduce the mucus blockage of the lung's airways.

Chest therapy consists of bronchial, or postural, drainage, which is done by placing the patient in a position that allows drainage of the mucus from the lungs. At the same time, the chest or back is clapped (percussed) and vibrated to dislodge the mucus and help it move out of the airways. This process is repeated over different parts of the chest and back to loosen the mucus in different areas of each lung. This procedure has to be done for children by family members but older patients can learn to do it by themselves. Mechanical aids that help chest

physical therapy are available commercially. Exercise also helps to loosen the mucus, stimulate coughing to clear the mucus, and improve the patient's overall physical condition.

Medications used to help breathing are often aerosolized (misted) and can be inhaled. These medicines include bronchodilators (which widen the breathing tubes), mucolytics (which thin the mucus), and decongestants (which reduce swelling of the membranes of the breathing tubes). A recent advance, approved by the Food and Drug Administration, is an inhaled aerosolized enzyme that thins the mucus by digesting the cellular material trapped in it. Antibiotics to fight lung infections also are used and may be taken orally or in aerosol form, or by injection into a vein.

- Management of digestive problems

The digestive problems in CF are less serious and more easily managed than those in the lungs. A well-balanced, high-caloric diet, low in fat and high in protein, and pancreatic enzymes (which help digestion) are often prescribed. Supplements of vitamins A, D, E, and K are given to ensure good nutrition. Enemas and mucolytic agents are used to treat intestinal obstructions.

Gene Therapy—The Future of CF Treatment?

Gene therapy for CF is not yet possible but impressive progress is being made in developing ways to treat the gene abnormality that causes CF. In the laboratory, scientists have been able to grow cells from the nasal passages of CF patients. By introducing the normal gene into these cells, researchers corrected the cells' chloride transport abnormality. The chloride defect has also been corrected in small regions in the nasal passages themselves by giving CF patients the normal gene in nose drops.

Scientists are still looking for answers to many questions about gene therapy. Some of these questions are: How should the gene be packaged? What are the best ways to get the gene-containing package into the patient's lungs? What will the long-term results of this treatment be? Can the abnormal chloride transport be corrected in other parts of the body? How long will the correction last? And, most importantly, can gene therapy cure or prevent the lung disease in CF?

Is It Possible to Detect CF in an Unborn Baby?

Finding out whether a baby is likely to have CF is possible using prenatal genetic tests. However, the tests cannot detect all of the CF gene mutations. Also, because these tests are very expensive and have certain risks to the mother, they are not used for all pregnant women. If there is another child with CF in the family, the expectant mother may request a prenatal test to see if the fetus has CF genes from both parents, is a carrier for one gene, or is altogether free of the CF genes.

There are two special prenatal tests

HOW DOES THE GENE MUTATION CAUSE CF?

The CF gene was identified in 1989. Since then, a great deal has been learned about this gene and its protein product. The biochemical abnormality in CF results from a mutation in a gene that produces a protein responsible for the movement through the cell membranes of chloride ions (a component of sodium chloride, or common table salt). The protein is called CFTR—cystic fibrosis transmembrane regulator.

CFTR is present in cells that line the passageways of the lungs, pancreas, colon, and genitourinary tract. When this protein is abnormal, two of the hallmarks of CF result—blockage of the movement of chloride ions and water in the lung and other cells and secretion of abnormal mucus.

The mutation involved in CF causes the deletion of three of the base pairs in the gene. This in turn, causes a loss in the CFTR protein of an amino acid (the building blocks of proteins). Because phenylalanine is located in position 508 of the protein chain, this mutant protein is called ΔF508 CFTR.

However, ΔF508 CFTR accounts for only 70-80 percent of all CF cases. Various other mutations—over 400 at the last count—seem to be responsible for the remaining CF cases. Differences in disease patterns seen in individuals and families probably result from the combined effects of the particular mutation and various, but still unknown, factors in the CF patient and his or her environment.

that can be done—either an amniocentesis or chorionic villus biopsy will be performed. In amniocentesis, cells from the fluid surrounding the baby in the mother's womb (called the amniotic fluid) are tested to see if the CF genes common to the parents are present. In chorionic villus biopsy, cells from the tissue that will eventually form the placenta are tested for the CF gene.

Can CF Be Prevented?

At this time, preventing CF is not possible. In babies with two abnormal CF genes, the disease is already present at birth in some organs, such as the pancreas and liver, but develops only after birth in the lungs. Someday, gene therapy may be used to prevent the lung disease from developing.

Yet, CF might be prevented in the future. Since CF occurs only when both parents pass on a CF gene to a child, it could be prevented by identifying all carriers of CF genes. Genetic counselors might then persuade couples who are carriers not to have children. However, as noted, current tests can detect only some of the more than 400 gene mutations and so the tests are only 80-85 percent accurate.

Yet, progress in gene therapy and the realization that not all CF mutations are life-threatening should reassure couples. Potential parents who carry the defective gene may choose to have children.

How Can Patients and Their Families and Friends Be Helped To Cope with CF?

CF education helps patients and their families face the physical and emotional effects of the disease and encourages CF patients to lead active, fulfilling lives. Educational programs and materials suitable for both patients of various ages and their parents are available from local CF centers and from local chapters of the CF Foundation.

Patients and their families and friends should know that:

- CF parents should not feel guilty or responsible for causing their child's disease; they could not have prevented it.
- Parents should treat their children with CF as normally as possible. They shouldn't be over-protective but should encourage them to be active and self-reliant.
- Family and friends should remember that CF is not contagious; nobody can get it from a patient.
- In families with CF, brothers, sisters, and first cousins of the CF patient should be tested to see if they carry a defective gene, especially if they seem to have a chronic lung or digestive problem. Carriers of the abnormal gene should get genetic counseling.
- Individuals with CF have normal sexual development and can expect to have a normal sex life. However, most, but not all, men are infertile because of a mechanical blockage of sperm and cannot have children. Women with CF can have children, although they may be less fertile than women without CF.
- Patients and families should work closely with doctors and other medical specialists to develop self-management skills that can improve their quality of life.

Above all, CF patients and their families should keep a positive attitude. Scientists continue to make significant advances in understanding the genetic and physiological disturbances in CF and in developing new treatment approaches such as gene therapy. The outlook is bright for further improvements in the care of CF patients and even for the discovery of a cure.

FOR MORE INFORMATION

Additional information about CF can be obtained from the following organizations:

National Heart, Lung, and Blood Institute (NHLBI) Information Center

P.O. Box 30105
Bethesda, MD 20824-0105
Telephone: 301-251-1222

The Cystic Fibrosis Foundation

6931 Arlington Road, #200
Bethesda, MD 20814
Telephone: 301-951-4422
1- 800-344-4823

National Diabetes Information Clearinghouse

1 Information Way
Bethesda, MD 20892-3560
Telephone: 301-654-3327
1-800-891-5388

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