

# Cystic Fibrosis

## Occurrence of cystic fibrosis

Cystic fibrosis is a non-infectious disease. It affects mainly the Caucasian population and the Genzyme Corporation statistics are: "Your chance of being a CF carrier is: Caucasian -1/25; Ashkenazi Jewish -1/26; Hispanic-1/46; African American-1/65 Asian American-1/90"<sup>1</sup>.

"Each year approximately 3,200 white babies are born in the United States with CF. The disease is much less common among black and Asian-American children. Two-thirds of the infants born with CF will be diagnosed in the first year of life. In all, about 30,000 American adults and children are living with this disorder."<sup>2</sup> Those figures were taken from FightCF.com, and its accuracy could be questioned, as they do not refer to any specific statistics. Yet it gives a good overall idea of how many individuals approximately are affected by cystic fibrosis.

Cystic Fibrosis Australia claims that cystic fibrosis affects one in every 2,500 babies. These statistics would give a good idea of how many people are affected by cystic fibrosis. These statistics and data are relevant because it shows to what extent cystic fibrosis affects a normal population. In Australia (except for Western Australia), all babies are screened for cystic fibrosis at birth. Because cystic fibrosis is a genetic disorder, there is no particular region(s) in the world that is affected. However, it is more predominant in various races as detailed by the statistics above.

Currently there is no comprehensive database that covers the extent of cystic fibrosis throughout the world, although there are smaller national databases that are accurate only for the country or area they detail. However, because cystic fibrosis is a non-infectious disease, it is not necessary to contain a database which gives the overall numbers in the world. The current databases are extremely efficient and detailed and can be used to predict and analyse trends for countries.

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<sup>1</sup> Genzyme Corporation (genzyme.com)

<sup>2</sup> FightCF.com

## Symptoms of cystic fibrosis

Cystic fibrosis affects the glands that produce mucus, tears, sweat, saliva and digestive juices. In a person who does not have cystic fibrosis, these secretions are slippery and thin, but an affected individual will have thick and sticky secretions. These means that instead of acting as a lubricant for internal body surfaces and tissues, the secretions generally tend to clog up tubes, ducts and passageways. This is especially true for the lungs and the pancreas. Consequently, respiratory failure is the most dangerous consequence of cystic fibrosis.

The symptoms of cystic fibrosis occur very early in life. In newborns, the first sign is usually a blockage of the intestines. The blockage of intestines is usually denoted by no production of stools in the first 48 hours of life. This occurs because the black stools normally passed by a newborn in the first day or two becomes thick and cannot move through the intestines. In infants, other common symptoms include lack of growth, large and bulky stools and frequent respiratory infections.

Other symptoms that can be present in children young teenagers include:

- An extremely salty taste to the skin due to increased levels of sodium chloride in sweat
- Frequent bowel blockages
- Foul smelling and greasy stools
- Lack of growth, or delayed growth
- Constant chronic coughing or wheezing
- Growths in the nasal passages
- Clubbing (rounding/enlargement) of the fingers and toes
- Part of the rectum protruding through the anus (due to the difficulty in passing stools)
- Frequent lung and chest infections
- Cirrhosis of the liver due to inflammation of bile ducts
- Displacement of one part of the intestine into another part (intussusception)

Cystic fibrosis also affects the pancreas. This is because the pancreas control the level of sugar present in the blood and approximately 7% of people with cystic fibrosis develop type 1 diabetes. The bile duct can also be inflamed and blocked, causing liver problems as mentioned earlier.

In addition to affecting the lungs, airways and pancreas, cystic fibrosis also affects the reproductive systems in both males and females. In males, thick secretions block the tube connecting the testes and prostate gland, leading to infertility. The majority of men with cystic fibrosis are infertile, but certain fertility methods and surgical procedures can allow cystic fibrosis men to become. Women also can be less fertile, but there are known cases where women with cystic fibrosis have conceived children and had successful pregnancies.

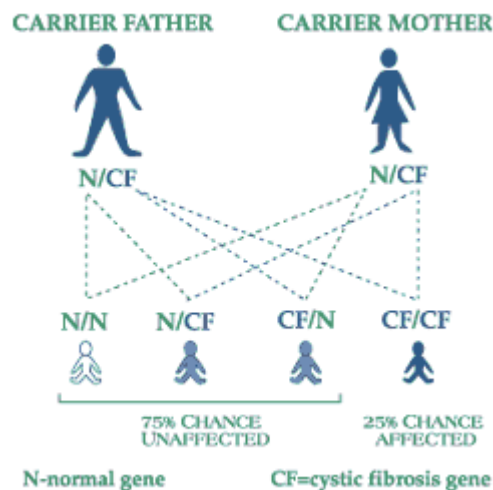
## Cause of cystic fibrosis

Cystic fibrosis is caused by a defective gene on chromosome 7. This defective gene leads to the alteration of a protein that regulates the movement of the salt sodium chloride both in and out of body cells. This gene is known as the CFTR gene and was discovered in 1989 by Collins and Tsui at Yale University.

Since the discovery of the CFTR gene, the much progress has been made in learning more about the cause of cystic fibrosis. As the researchers examined the CFTR gene, they discovered that it consisted of 27 segments of DNA that code for different parts of a protein. All cystic fibrosis individuals had an error or mutation in the CFTR gene. Despite the fact that only three base pairs of the 250,000 base pairs were missing, it was enough to disrupt the normal functioning of the individual. This absence of three pairs corresponds to just one amino acid in the chain of 1480 amino acids.

While cystic fibrosis can be caused by around 600 different mutations, a few of the mutations account for many cystic fibrosis individuals. The mutations include promotor mutations, frameshift mutations, initiation and translation problems, mRNA splicing mutation and the changing of the base pairs to form a stop codon.

The inheritance of the defective gene is autosomal recessive. The diagram below illustrates the inheritance of the disease. Both parents must be carriers for any of their children to be affected. The simple diagram below illustrates the outcomes of the children if both mother



and father are carriers of a defective CFTR gene.

A mutation in the cystic fibrosis gene will cause an alteration of the protein that regulates the movement of sodium chloride in and out of cells. This protein is known as the CFTR (cystic fibrosis transmembrane conductance regulator) protein. The CFTR protein is a chloride channel protein which is regulated by cyclic AMP (cAMP). From the specific example of the CFTR protein and cystic fibrosis, the links between gene expression and the maintenance and repair of body tissues becomes evident. A defect in the genetic coding (DNA) leads to a change in the gene expression which leads to the cause of a genetic disorder.

The CFTR protein is found in the cell membrane, and channels chlorides in and out of the cells. This is important because it retains osmotic balance and acts as a chloride channel. The CFTR protein is found predominantly in cells lining the lungs, airways and pancreas. This accounts for the effect and symptoms of the disease cystic fibrosis. The most

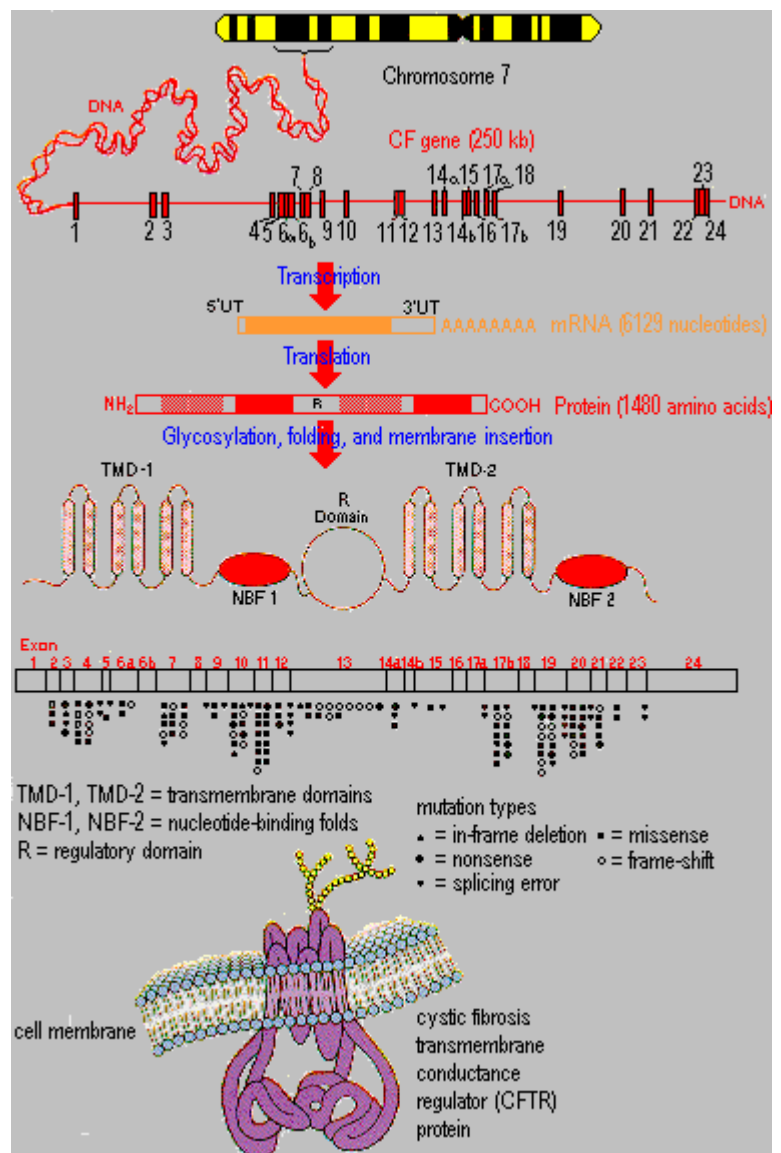
common cause of cystic fibrosis is the mutation "DeltaF508 deletion ". This is shown in the diagram below:

In Normal CFTR:							
Nucleotide	AAT	ATC	ATC	TTT	GGT	GTT	TCC
Amino Acid	Asn	Ile	Ile	Phe	Gly	Val	Ser
	505			508			511

In ΔF508 CFTR:						
Nucleotide	AAT	ATC	ATC	GGT	GTT	TCC
Amino Acid	Asn	Ile	Ile	Gly	Val	Ser
	505					

The diagram to the right shows how a mutation in the cystic fibrosis gene can cause cystic fibrosis. When the transport of chloride is affected especially in the airways and lungs, it causes a buildup in sputum and mucus, which is the main symptom for cystic fibrosis.



## Treatment/management of cystic fibrosis

Cystic fibrosis can be treated in many ways, but in a sense it cannot be cured; it is a life-long illness. However, there are many treatment or management strategies that allows the cystic fibrosis individual to lead more normal lives. The main priority in treatment strategies is to treat infections, improve airflow, keep the lungs free of sputum and maintain a suitable diet.

There are many treatments for cystic fibrosis which include:

- Antibiotics

The antibiotics that are ingested into the affected individual will kill the bacteria that cause lung infections. This leads to a lower rate of lung infections which means the individual is not "sick" all the time. Oral and intravenous antibiotics are commonly used. However, new aerosolised antibiotics are inhaled, and provide the antibiotics and medication directly into the airways. There is ongoing research into the use of aerosols as a medium for the use of antibiotics in cystic fibrosis individuals. For example, the University of North Carolina recently conducted a clinical trial which had two main objectives:

"I. Determine the stability of uridine triphosphate (UTP) and examine the metabolism of exogenous nucleotides on airway epithelial surfaces in patients with cystic fibrosis.  
II. Determine the acute safety and efficacy of aerosolized UTP in children with cystic fibrosis"<sup>3</sup>

This study reveals that aerosol sprays are still under development as they can be possibly be potentially harmful to children affected by cystic fibrosis. Another disadvantage of using antibiotics frequently to fight lung infections is that the bacteria can eventually become resistant to the antibiotics, which is a potential danger for many.

- Mucus-thinning drugs

As one of the main problems associated with cystic fibrosis is the buildup of mucus, various drugs have been developed to combat this problem. When DNA is released due to the white blood cells fighting bacteria in the airways, it thickens the mucus. One drug that has been developed is Pulmozyme which is basically an enzyme that fragments the DNA, making the mucus thinner and easier to cough up. However, like antibiotics the drugs can be useful but often have disadvantages; in this case side effects such as a sore throat and chest irritation.

- Bronchial airway drainage procedures

As previously mentioned, cystic fibrosis causes the buildup of thick mucus in the lungs and airways. Apart from the mucus-thinning drugs a more simple way to effectively remove the mucus is to stimulate the person to cough it up. Generally this is done by manually clapping the front and back of the chest, while other cases use an electric

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<sup>3</sup> Objectives taken from Clinical Trials, the National Institute of Health (January 1999)

chest clapper or mechanical percussor. Cystic fibrosis individuals, both adults and children require at least 2 sessions of bronchial airway drainage for at least 20 minutes.

- **Oral enzymes and improved control over nutrition.**

When the pancreatic enzymes for digestion do not reach the small intestines due to the blockage, it often causes malnutrition. This may result in the individual needing up to twice the calories than if they were not affected by cystic fibrosis. As a result, oral pancreatic enzymes are often used to supplement, and are commonly taken in the form of tablets before meals, along with various other special vitamins.

- **Oxygen Therapy**

This treatment involves the delivering of oxygen to the individual. This makes it easier for the cystic fibrosis individuals to breathe and loosen up the mucus. The oxygen is stored as compressed gas, liquid oxygen or by using an oxygen concentrator. The oxygen is delivered by a mask, or a two pronged nasal cannula that provides oxygen into the nasal passage.

The treatment and management methods and strategies mentioned above deal only with the symptoms of cystic fibrosis. Current research into gene therapy could be the next "cure" for cystic fibrosis.

Along with the treatment methods, there are many other steps which can greatly assist cystic fibrosis individuals, especially with children, as they are prone to infection and illnesses. These include:

- Keeping the child's vaccines up to date
- Use clean hygienic practices eg. hand washing
- Eliminate smoking around affected children
- Emphasising liquids to the child; encouraging him or her to drink lots of liquids which assist in loosening mucus
- Using nutrition supplements; especially for pancreatic enzymes

## The shift in emphasis from treatment and control to management or prevention of the disease

Previously, individuals affected with cystic fibrosis did not live beyond their teens, due to the lack of knowledge about the cause of the disease. However, since that time, researchers and scientists have made progress in discovering what causes cystic fibrosis and the symptoms associated with this. As a result, cystic fibrosis is now often diagnosed early on in life, which can allow for improved and consistent treatments for the disease. This means that affected people now live much longer lives, most of them reach their 30s, while also enjoying comfortable and satisfying lives.

Since the discovery of the cystic fibrosis gene in 1989, there has been a shift in the emphasis of treatment and management of cystic fibrosis, to a increased understanding in the genetics behind cystic fibrosis. While cystic fibrosis cannot be prevented, early detection of a defective cystic fibrosis gene allows parents to prepare for a child with cystic fibrosis, or even terminate the pregnancy if they deem appropriate.

"Patients and clinicians have witnessed dramatic gains in the survival of people with CF – with the median age of survival improving from 14 years in 1969 to 32 years in 2002"<sup>4</sup>. This data was taken from a newsletter released by one of the subsidiaries of the Cystic Fibrosis Foundation, and its accuracy can be justified, as those figures are taken from CF Foundation Patient Registry. As the newsletter claims, "Through the CF Foundation Patient Registry Annual Data Report, these differences can be adequately assessed and trends can be established. The registry also has been extremely important in regard to the effective design of CF clinical trials. In addition, the registry is used to calculate the number of patients needed for a research study to ensure statistically meaningful results." Such a large database on cystic fibrosis individuals allows the Cystic Fibrosis Foundation to report on particular characteristics common throughout the cystic fibrosis population, general trends and the frequency and impact of various treatment programs. This shows a changing emphasis in merely attempting to treat cystic fibrosis cases as they appear to a more efficient way of collecting data regarding cystic fibrosis to aid in future cases.

The detection of a mutant cystic fibrosis gene and the associated decisions is known as genetic counselling. This is often used by couples who have had a family history of cystic fibrosis.

Now there is a major emphasis on the early diagnosis and detection of cystic fibrosis. There are many tests available to diagnose cystic fibrosis which include:

- **Sweat chloride test**

**This test has been used for over 40 years, and is considered an extremely**

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<sup>4</sup> February 2002 Cystic Fibrosis Services "Homeline" newsletter- Christopher H. Goss, M.D., M.Sc., and H. Worth Parker, M.D.

**reliable and accurate test. It is the best test to diagnose cystic fibrosis when performed by professionals and analysed and evaluated by experience laboratory technicians. This test is universal in that it can be performed on any individual at any age.**

**The sweat chloride test analyses the amount of chloride present in a sweat sample.** This is done by applying a small amount of a colourless, odourless chemical which is followed by the application of a weak electric current through an electrode to stimulate sweating. The second part of the test consists of cleaning the stimulated area and collecting the sweat on a piece of filter paper or gauze or in a plastic coil. The sample is taken to a hospital laboratory and analysed. This sweat test is performed twice to obtain reliable results.

The amount of chloride present in the sweat sample is an extremely accurate indicator of if the person is affected by cystic fibrosis. Values below 40 mmol/L indicate that the person is not affected by cystic fibrosis. Sweat chloride concentrations greater than 60 mmol/L indicate that the person is affected by cystic fibrosis. Values between 40 and 60 mmol/L are considered borderline values and additional tests may need to be carried out.

This test is extremely effective and accurate because it is not affected by illness, or recent activities or diets.

- Immunoreactive trypsin (IRT)

This test is used as an alternative to the sweat chloride test especially for young infants. Young infants usually cannot produce enough sweat to be analysed, and IRT is used as an alternative. It is usually used as an initial test if the infant does not produce stools in the first 48 hours of life. The test involves analysing the production of trypsinogen. However, IRT is not as conclusive as the sweat chloride test and there are quite a few false positives that can be detected and problems not caused by cystic fibrosis along with pancreatic dysfunctions can cause a positive IRT result.

If the IRT level is elevated, the infant may have cystic fibrosis. Most results are reported as numerical values, and compared against reference range data. If the test is positive and the physicians suspect cystic fibrosis, other tests will have to be carried out.

IRT testing will not identify cystic fibrosis carriers as the production of trypsinogen is not affected in carriers.

- Blood chloride test

Similar to the sweat chloride test, the samples are taken from the blood. This is especially useful in infants who cannot produce enough sweat. The blood can also be analysed genetically to determine if there are any mutations present on the cystic fibrosis gene.

Many of the tests above only detect certain mutations in the cystic fibrosis gene. Testing has been developed for approximately 30 mutations, which cause the majority of the cases of cystic fibrosis. This correlates to approximately 90% of cystic fibrosis cases. As a result, the tests in general are fairly accurate.

Genetic counselling allows couples to learn about the genetics that cause cystic fibrosis. Because cystic fibrosis is a genetic disorder, some couples are tested to determine if they are carriers of the mutant cystic fibrosis gene. This is because the mutant cystic fibrosis

gene is an autosomal recessive gene. This means that the cystic fibrosis individual has inherited one mutant gene from each parent. Conversely, each parent must be a carrier for any children to be affected by cystic fibrosis. **Generally, carrier testing is only carried out if the family has a known history of cystic fibrosis.**

There are two main tests to determine if the child will have cystic fibrosis:

- Chorionic villus sampling (CVS)  
This test is generally carried out during the 11th week of the pregnancy and involves using a small instrument which removes a very small part of the placenta.
- Amniocentesis  
**This test is carried out later on in the pregnancy, around the 16th week. It is performed by removing a small amount of fluid surrounding the baby, through a small thin needle inserted into the mother's uterus.**

**These prenatal tests are nearly 100 percent accurate as to whether or not the baby will be affected by cystic fibrosis.**

When a baby is detected with cystic fibrosis, generally there are two options available:

- "1. Continue the pregnancy and prepare for the addition to your family of a child with CF.
2. Terminate the pregnancy."<sup>5</sup>

These two options are the only ones that can be taken as cystic fibrosis is not a curable disease, and if the couple decides to continue with the pregnancy, constant medication will be required throughout the child's life.

As detailed above, it can be seen that there has been a strong shift in the emphasis from treating the symptoms to diagnosing cystic fibrosis early on in life. When cystic fibrosis is diagnosed early on in life, it gives the parents time to learn to cope with it, and essentially allows the child to learn to live with cystic fibrosis and to adjust with all the medications and required medical attention and procedures.

As mentioned earlier, cystic fibrosis cannot be "prevented" because it is a genetic disease, but when parents are more informed about cystic fibrosis it allows them to make informed choices when deciding to make a family. The genetic counselling is extremely informative to couples and helps them make the right decisions. This change from treatment to prevention will not necessarily make the rate of cystic fibrosis drop, but it is important as it reflects our increased understanding of genetics and its implications on society.

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<sup>5</sup> The American College of Obstetricians and Gynecologists Patient Education Pamphlet

## Gene therapy and cystic fibrosis

Gene therapy is an alternative to the previous treatment methods mentioned. However, gene therapy is still in its infancy compared to the use of antibiotics and mucus-thinning drugs. Despite this, gene therapy is extremely important and many institutions around the world are currently researching into the use of gene therapy to treat cystic fibrosis.

As recently as 29 April 2003, the University Hospitals of Cleveland (UHC), Case Western Reserve University (CWRU) School of Medicine, Children's Hospital of Denver, and Cystic Fibrosis Foundation Therapeutics, Inc., have announced extremely encouraging results about the use of gene therapy in cystic fibrosis.<sup>6</sup> "This gene therapy research has exciting potential as a new approach to addressing the genetic root cause of CF," said Robert J. Beall, Ph.D., president and chief executive officer of the Cystic Fibrosis Foundation". As Robert Beall explained, gene therapy will be ultimate way to treat cystic fibrosis.

In the year long clinical trial, researchers formulated a way of compacting the tightly wound DNA so that is could be small enough to penetrate the cell and nuclear membranes, making its way into the nucleus. This would trigger the production of the correct chloride protein. By dripping a saline solution containing the healthy gene into the patient's nasal passages, investigators noticed a difference in the increase of transport of chloride in the nasal passages. This technology could be extended to provide the healthy gene directly to the lungs and airways. According to the results of the trial, the new method showed that the gene transfer had indeed occurred.

Further research will be needed to make this method of therapy useful and effective. "Gene transfer technology is expected to revolutionize treatment of genetic disease by using DNA as a novel therapeutic," said Jeff Wagener, M.D., Professor of Pediatrics at the Children's Hospital of Denver; this is because it treats the root of the cystic fibrosis disease, and not just the side effects or symptoms of the disease.

Currently, the type of gene therapy being used is somatic gene therapy as opposed to germ cell gene therapy. Unlike other diseases, gene therapy could be extremely useful because cystic fibrosis is a genetically inherited disease, and is due to the mutation of the cystic fibrosis gene.

Research is continuing into the possibility of delivering a "normal" gene into the affected cells that line the airways and lungs. Several methods have been developed and tested by using clinical trials. These include:

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<sup>6</sup> Public release: "Cystic Fibrosis Gene Therapy Trial Results Encouraging" (April 29, 2003)

- **Viral vectors**

Currently, research is being undertaken to harness the ability of the virus to inject genetic material into body cells and force the cell to reproduce the genetic material. As cystic fibrosis is caused by the mutated gene, using viruses to deliver the "normal" gene could be extremely effective. "Take two killers"<sup>7</sup>, an article published by the *New Scientist*, describes and evaluates the work of scientists in the University of Pennsylvania in Philadelphia to produce an effective viral vector.

In their research, the scientists used two deadly viruses as a means of delivery. They used the HIV virus, as it is extremely effective in infecting cells, even if they don't divide. This is because they integrate themselves into the cell's chromosomes. The HIV virus could be extremely useful because cells lining the airways and lung do not divide often. However, the HIV virus is not that effective in infecting lung tissues, so researchers used various respiratory viruses, including influenza and the deadly Zaire strain of Ebola. These respiratory viruses have the right type of enveloping proteins that could revolutionise the delivery of genetic material to the airways and lung tissues. Some critics are worried that this could be dangerous by using two deadly killer viruses. But Pamela Davis, a cystic fibrosis researcher at Case Western Reserve University in Cleveland, Ohio says, "It's a novel approach that definitely delivers the gene payload to the lung". This can be justified because the hybrid virus is safe as it is the crippled version of the HIV and various respiratory viruses.

Such research is extremely promising and *New Scientist* reported that, "(the researchers) found that the hybrid infected at least eight times as many cells as any other virus they tested. Tests on live mice showed that 63 days after exposure to the virus, the marker gene was still active in 24 per cent of lung cells."

- **Fat capsules (liposomes)**

The healthy gene is contained in the liposome which is transferred directly into the patient's lungs and airways.

Gene therapy will be the next way of treating cystic fibrosis and it, when fully researched and developed, will revolutionise the lives of those affected by cystic fibrosis. Until that time, cystic fibrosis individuals will continue to take the temporary medicines that are needed to fight off infections and lessen the side effects.

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<sup>7</sup> *New Scientist* vol 169 issue 2281 - 10 March 2001, page 19

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