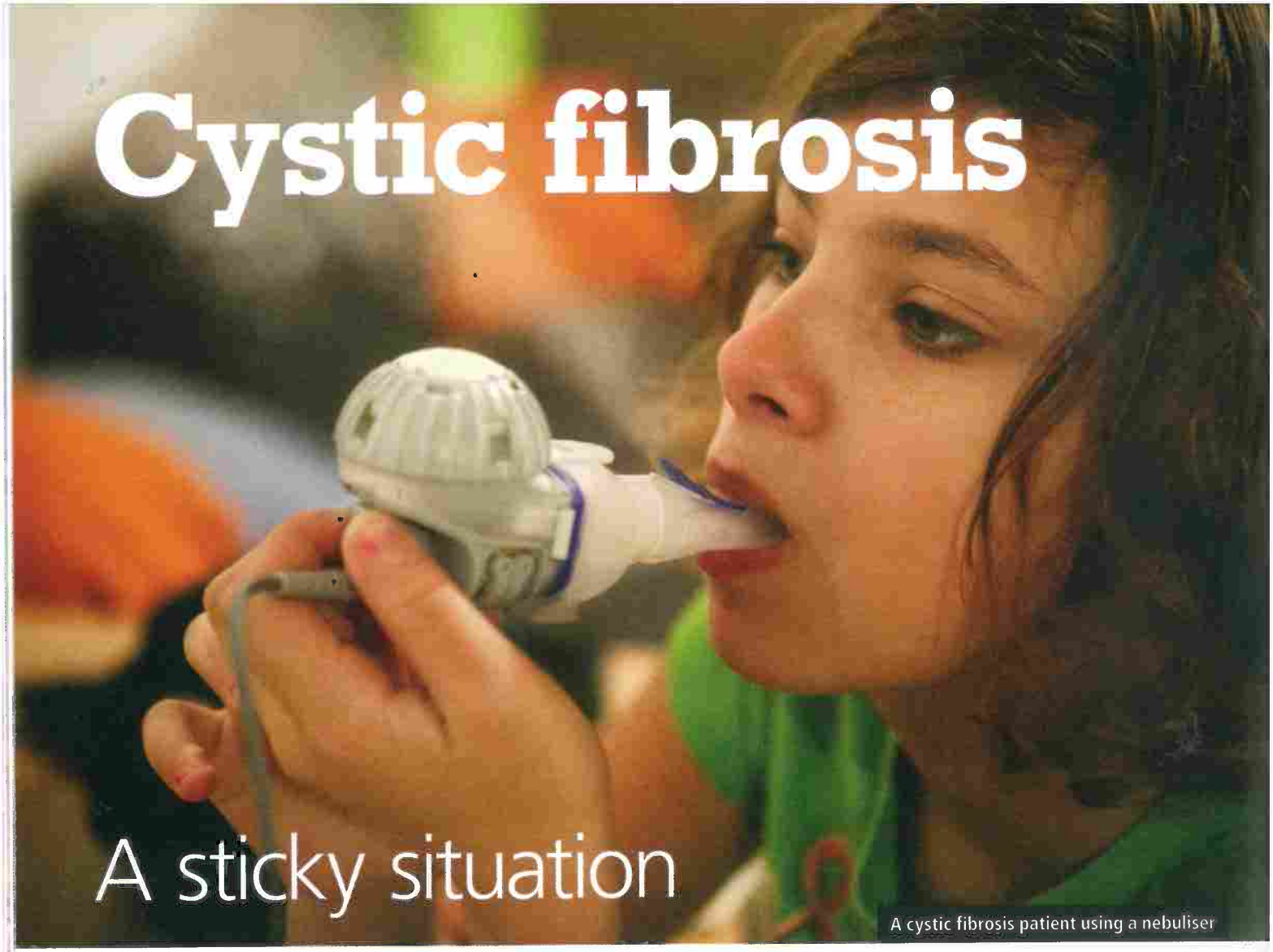
Cystic fibrosis

A sticky situation



A cystic fibrosis patient using a nebuliser

Laurie Smith and Alex Horsley

Breathing is something most of us seldom think about. In, out, in, out — we breathe about 15 times every minute, over 20000 times in 24 hours. But when someone's lungs are damaged, in diseases such as cystic fibrosis, they become breathless and can die of progressive lung failure. Respiratory experts Laurie Smith and Alex Horsley explain how understanding lung disease is vital in modern respiratory healthcare

Key words

Alveoli
Mucus
Lung
Cilia
Cystic fibrosis

Breathing is a complex process. When air first enters our bodies, via the nose and mouth, it passes into the trachea — a large rigid airway surrounded by rings of cartilage. The trachea splits into two branches — the bronchi — one to each lung. Each bronchus then divides into two further airways, which divide and divide again into smaller airways called bronchioles. At the end of the airways are membranes that form clusters of small sac-like structures called alveoli (see Figure 1). The alveoli are where oxygen (O_2) is taken up by red blood cells, passing through capillaries — narrow blood vessels that surround the alveoli. At the same time, carbon dioxide (CO_2) passes from red blood cells into the alveoli to be breathed out. The barrier between air and blood is extremely thin (0.3 micrometres), and the branching nature of the lungs provides a vast surface area for gas exchange — approximately the area of a tennis court.

Diseases that affect the airways, the alveoli, the blood vessels or the respiratory muscles can all reduce the efficiency of O_2 and CO_2 exchange and cause the patient to feel breathless. A respiratory physiologist is a healthcare professional who assesses the lungs of people with respiratory disease using a variety of breathing tests performed at rest and during exercise. These tests measure how damaged lungs are, monitor disease progression and assess how patients respond to treatment. These tests both diagnose lung disease and monitor its progression.

What is cystic fibrosis?

Cystic fibrosis (CF) is an inherited disease that affects one in 2500 live births in the UK. It is caused by inheritance of a faulty gene, which leads to either a deficiency or absence of a protein called the cystic fibrosis transmembrane conductance regulator (CFTR). CFTR controls the movement of chloride and sodium ions across cell membranes. Since water follows these ions across cell membranes, CFTR is an important regulator of water movement and hydration of cell surfaces. One in every 25 people has a faulty copy of the gene as well as a normal copy (these are **heterozygotes**), but CF does not occur unless two copies of the faulty gene are inherited (these people are **homozygotes**). CF is therefore a **recessive** genetic condition.

Effects of cystic fibrosis on the lungs

A thin layer of mucus lines the airways of healthy lungs (see Figure 2). Mucus is a complex mixture of water, ions, proteins and large sugar-coated molecules called mucins, which give mucus its 'sticky' nature (see Biological Sciences Review, Vol. 27, No. 3, pp. 22–26). There are small hair-like structures, called cilia, on the surface of epithelial cells lining the large airways. The cilia beat in a rhythmic fashion to move mucus up through the trachea and into the mouth to be swallowed, thus eliminating the bacteria and particles trapped in the mucus layer, keeping our airways clean.

In CF, the cell surface dehydrates due to the lack of functional CFTR. In this dehydrated environment, cilia cannot beat properly and mucus is more viscous. This results in mucus building up and ultimately blocking the airways. This sticky mucus also provides an ideal environment for bacteria to inhabit, causing infection in the airways. When this happens the airways become inflamed as the body responds. The inflammatory response causes the airway walls to thicken, which causes them to narrow. Inflammation leads to more mucus being produced and the bronchioles fill up with both mucus and **neutrophils**. Repeated cycles of infection and inflammation cause widespread narrowing, blockage and destruction of the airways (see Figure 2).

Narrowing of the airways increases resistance to airflow in the lungs. The patient has to work harder to maintain a normal breathing pattern, and becomes increasingly more breathless. Inflamed and mucus-filled small airways may

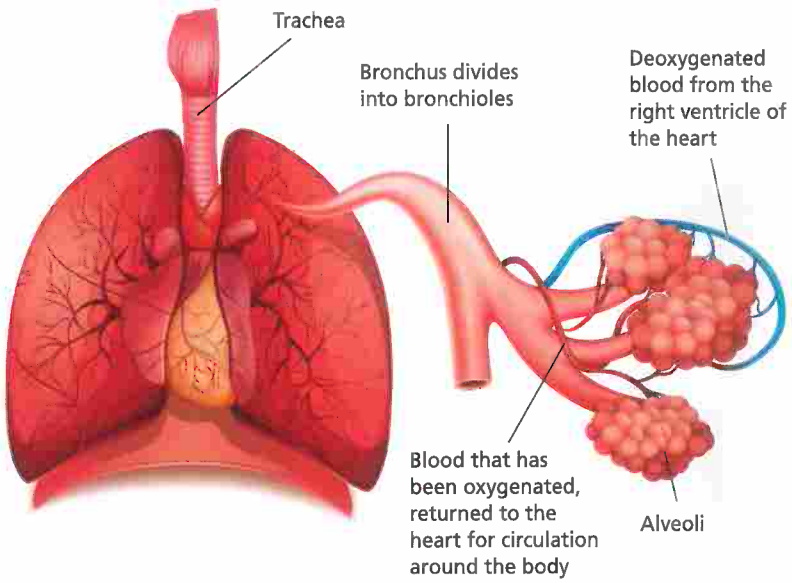


Figure 1 Structure of the lungs

Terms explained

Heterozygote An individual with two different alleles of a particular gene.

Homozygote An individual with two identical alleles of a particular gene.

Nebuliser A device that delivers an aerosol that is breathed directly into the lungs.

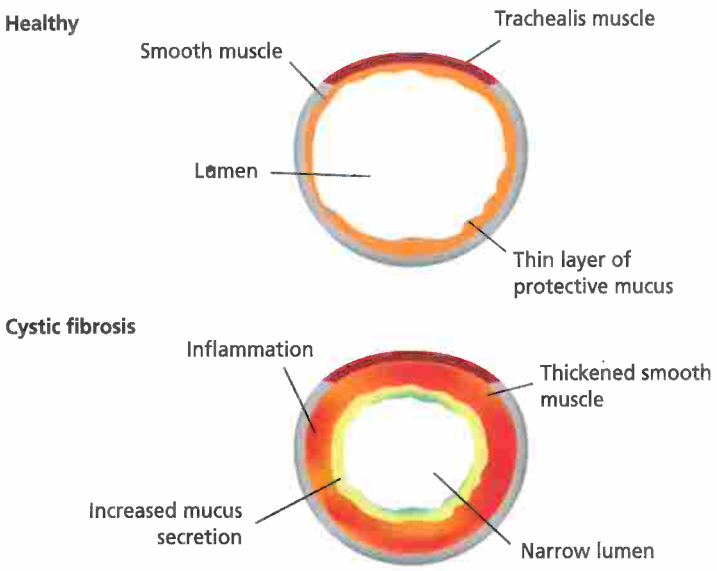
Neutrophil A type of white blood cell that ingests and destroys invading microorganisms and clears cell debris.

Recessive Two copies of a recessive allele must be present for its phenotype to be expressed.

Spirometry Lung function test to determine how well a person breathes in and out. A spirometer is the device used to take the measurements.

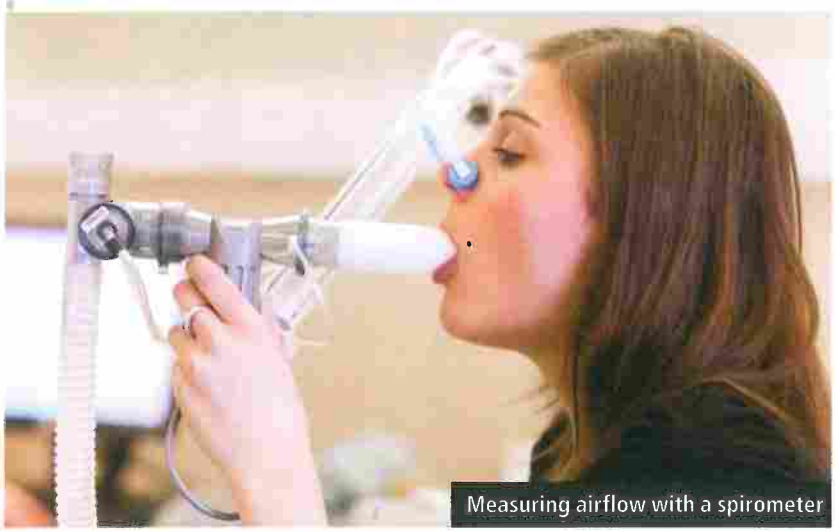
Transcription The first step of gene expression in which a particular segment of DNA is copied into RNA by the enzyme RNA polymerase.

Translation Follows transcription in the process of protein synthesis. The genetic code carried in RNA is decoded to produce the specific sequence of amino acids in a polypeptide chain.



- Narrowed lumen increases airway resistance
- Mucus causes chronic cough
- Inflamed airways eventually become scarred and changes irreversible

Figure 2 Diagrams showing narrowed airways in the lungs of cystic fibrosis patients



Measuring airflow with a spirometer

block completely, causing air to become trapped in the lungs. Hyperinflated lungs prevent the diaphragm and respiratory muscles from working efficiently. If this process becomes severe, the lungs are not able to work properly, so O_2 levels in the body fall and CO_2 levels rise. Unchecked, this can lead to breathlessness and eventually death.

Measuring lung function in CF

The main breathing test used in patients with CF is **spirometry**. This involves the patient breathing out from full lungs as hard as possible into a machine that measures airflow. Patients must exhale all the air out of their lungs in one continuous breath. This test measures:

- forced vital capacity (FVC) — the total amount of air that the patient can exhale
- forced expiratory volume in 1 second (FEV_1) — how much air was exhaled during the first second

FEV_1 is currently the most widely used measure of CF lung function and is used to monitor how damaged or blocked the patients airways are. Figure 1.1 in Box 1 shows spirometry results for normal healthy lungs and for a CF patient with severe lung disease.

How is CF treated?

One treatment for CF targets lung infections and helps to remove sticky mucus. Treatments are usually started from birth to try to slow the onset and progression of the disease. Patients are prescribed antibiotics to help treat infections. Antibiotics may be given as tablets, through a vein directly into the blood, or via a **nebuliser**. Removal of sticky mucus is often aided by specialist physiotherapists who use a variety of breathing techniques (lung physiotherapy) to encourage the mucus to move (see Box 2).

Not just a disease of the lungs...

Although the focus of this article is on CF as a lung disease, it is worth noting that CF doesn't just affect the lungs. The CFTR protein is expressed on the surfaces of cells throughout the body, including in the gut. Absence of CFTR therefore causes poor absorption of nutrients in the intestines. Many CF patients also develop diabetes in adult life due to damage to the pancreas, the organ in the body responsible for producing insulin to regulate glucose levels in the blood. Patients with CF are affected from birth. However, survival for CF patients has increased remarkably over the last 50 years such that patients who would have died as children in the 1950s and 1960s can now live into their 50s. This is largely due to significant improvements in the treatments available (such as nutrition supplements, antibiotics, mucus-loosening therapies), which

Box 1 Assessing lung function

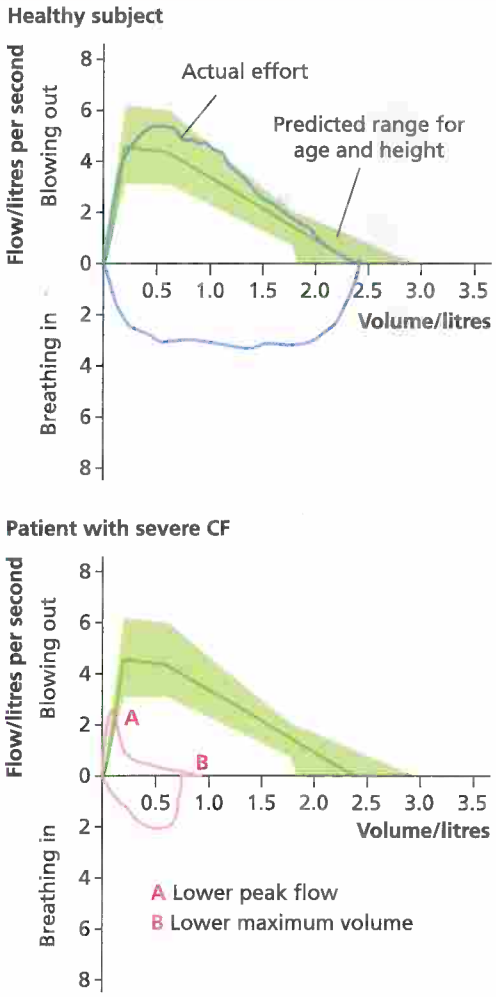


Figure 1.1 Spirometry results for normal healthy lungs and for a CF patient with severe lung disease

When a patient exhales forcefully, the airflow is greatest at the start and then falls off as the lungs empty. The blue line in the top graph shows a healthy subject's expiratory airflow (in litres per second (lps) on the *y*-axis against the volume of air expired in litres on the *x*-axis). The shaded green areas in these graphs show the expected range of normal for a subject of the same age, gender and height. The solid green line is the 'predicted' lung function curve. The CF patient (shown in pink on the lower graph) has a much smaller lung capacity (note the smaller maximum volume expired on the *x*-axis — approximately 0.8 litres of air compared with approximately 2.5 litres in a person of similar age), and is unable to blow out as fast (note the lower maximum speed of airflow — approximately 2.5 lps compared with approximately 5.5 lps in a person of similar age, on the *y*-axis). The concave shape to the expiration curve is typical of patients with severe CF lung disease, and represents the narrowed, blocked airways typical of CF.

are themselves due to better understanding of the mechanisms of the disease.

Looking forward...gene therapy for CF

Scientists have been working on gene therapy for CF almost since the gene responsible for the disease, the *CFTR* gene, was discovered in 1989. Lungs are relatively accessible organs so, in theory, we should be able to deliver a copy of the functional *CFTR* gene in the form of a nebuliser. Sadly it's not quite that simple. The *CFTR* gene is a long sequence of DNA that needs to be packaged and protected from the body's defence mechanisms. The gene must also be taken up by epithelial cells lining the airways and transported to the nucleus, where it can be **transcribed** and **translated** to make the protein, CFTR. Even if nebulised genes can overcome these barriers, and are successfully expressed so that the cells make CFTR, the cells are regularly replaced so the therapy needs to be repeated again and again.

Genes can be delivered in viruses that have been altered so that they cannot cause disease, or in artificial virus consisting solely of a layer of protective lipid. Both virus and lipid delivery vehicles need to be given repeatedly and there are challenges with both approaches. Viruses are more effective at getting the functional *CFTR* gene into lung cells but the body's immune system recognises the virus envelope as foreign and rapidly develops antibodies that recognise and destroy the virus if it is given again. Virus gene therapy therefore cannot be given repeatedly, and this is needed for a sustained production of working CFTR.

The UK Cystic Fibrosis Gene Therapy Consortium has just completed a major trial of gene therapy. This involved 130 people with CF receiving multiple repeated doses of an inhaled gene therapy agent for 12 months. The researchers have been trying to see if the functional *CFTR* gene is successfully expressed in the lungs of CF patients, how sustained the effect is, and what this does to their symptoms and lung physiology. The results of this trial are due to be reported later this year, and are eagerly awaited by patients and doctors.

Additionally, researchers in the USA have developed medicines that work directly in cells to help patients express their own CFTR. Unlike gene therapy, these drugs can be given orally but unfortunately they don't work against all *CFTR* gene variants. One such drug (Ivacaftor) is available for a small percentage of CF patients who have a specific change in CFTR which means that the cells make CFTR but it doesn't work properly. Others drugs are in development which may help many more CF patients.

Box 2 Therese: a patient's perspective on cystic fibrosis

Life with CF can be challenging and unpredictable. My day-to-day life involves the need to be organised, committed to treatments and staying active, while being flexible enough to accept that I may need to be admitted to a hospital unexpectedly. I take tablets to help me digest food, dietary supplements to replace the nutrients I don't absorb well enough from food, antibiotics to prevent chest infection, and sometimes steroids to reduce inflammation in my lungs. My lung treatments include daily inhalers, physiotherapy to clear mucus in my lungs, and nebulised antibiotics and mucus-thinning drugs. I also take insulin and monitor my blood sugars to control my diabetes. Sometimes, I need hospital admission for antibiotics into my blood stream, which is the strongest way to fight infection.

The happiest moment of my life was passing my medical finals and graduating as a doctor. I am glad I have the ability to understand what my patients are going through with their own chronic diseases. Little do they know that I face challenges of my own every day. CF has caused me many obstacles but I have been able to lead a normal, happy and fulfilling life so far and hopefully for many more years to come.

Therese at her internship at NASA. She is interested in space medicine and research, and won a scholarship to study at NASA

Further reading

Read, A. (2012) 'Gene therapy: are we nearly there yet?' Biological Sciences Review, Vol. 24, No. 4, pp. 2–5.

Herrick, S. (2013) 'Lung disease', Biological Sciences Review, Vol. 26, No. 1, pp. 6–10.

How to become a respiratory physiologist: **www.artp.org.uk**

More information on CF: **www.cysticfibrosis.org.uk**

Website for young people exploring CF and gene therapy: **www.changing-futures.co.uk**

Laurie Smith is a paediatric respiratory physiologist at Sheffield Children's Hospital and a research fellow at the University of Sheffield. Laurie is involved in assessing new methods for measuring lung function for cystic fibrosis patients. **Dr Alex Horsley** is a consultant specialist at the Manchester Adult Cystic Fibrosis Centre and a researcher at the University of Manchester. He cares for patients with cystic fibrosis and leads research into lung physiology to better understand the effects of cystic fibrosis and its treatments.

Key points

- At the end of the airways of the lungs are alveoli — tiny sack-shaped structures that afford the lungs an extensive surface area to enable efficient gas exchange.
- Cystic fibrosis is a genetic disease caused by inheritance of a faulty gene that encodes a non-functional protein present in cell membranes throughout the body, including the lungs.
- Cystic fibrosis patients suffer from progressive lung damage, which begins from birth and causes the patient to be breathless.
- Lung function is measured using a variety of breathing and exercise tests.