CYSTIC FIBROSIS

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Research into sequencing the human genome holds out the promise of better understanding, diagnosis and treatment of a wide range of hereditary diseases. Cystic Fibrosis (CF) is the most common such disease among Caucasians in the UK, and also the best-characterised example of a condition caused by the mutation of a single gene.

This briefing summarises recent developments in understanding, diagnosis and treatment of CF, and examines the issues that arise.

INTRODUCTION

CF is a disease that causes secretion of abnormally thick mucous, mainly affecting the lungs and digestive system. Symptoms (**Box 1**) are mainly related to blockages of the airways of the lung, resulting in chronic bronchitis and repeated bouts of pneumonia. Blockage of the pancreas also occurs, reducing the capacity of the gut to absorb food. CF also causes infertility in the majority of male sufferers.

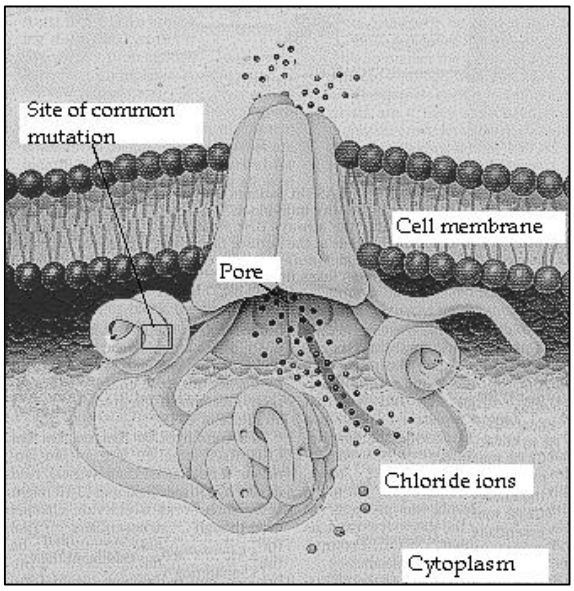
Life expectancy of sufferers varies depending upon which 'type' of the condition they have inherited (see later), with around half of all sufferers surviving past 30 years (although very few live beyond the age of 40). People with CF need daily treatment throughout their lifetime to alleviate breathing problems. Some 300 babies are born with CF each year in the UK, and this represents around one in every 2,500 births.

THE CF(TR) GENE

Only one of the 80,000 or so different genes in the body causes CF and then only when it is faulty. This gene is found on chromosome 7 of the human genome and codes for a protein found in epithelial (lining) cells, particularly those lining the surfaces of the lungs and the digestive system. Genes are translated into proteins inside cells, with the genetic code specifying the precise amino acid sequence (and thus function) of each protein. The normal, or healthy, version of the CF gene makes a protein which is located in the outer membranes of epithelial cells where it acts like a valve, channelling and regulating the passage of salts and water into and out of the cell (**Figure 1**).

This protein is called the Cystic Fibrosis Trans-membrane Conductance Regulator (CFTR) and the gene is thus known as the CFTR gene. People with CF inherit faulty copies of the gene from their parents, which means that their CFTR protein does not work properly and the passage of salts and water across epithelial cells is abnormal. Most of the symptoms in Box 1 stem from a reduction in the amount of water pumped across cell membranes. This results in the build up of thick, sticky secretions in the cells lining the lungs, pancreas and intestines, which in turn attracts bacteria and encourages infections.

FIGURE 1 THE CF PROTEIN



BOX 1 SYMPTOMS / DIAGNOSIS OF CF

Any child or young adult who has chronic lung disease or pancreatitis (inflammation of the pancreas) might be suspected of having CF. The most specific test for CF is a measurement of the amount of chloride (or salt) in the sweat. Symptoms commonly associated with the lung disease include:

- Chronic cough, sputum production;
- Difficulty breathing (especially with exercise);
- Recurrent pneumonia.

Digestive problems often include:

- Abnormal pale fatty stools;
- Gallstones;
- Jaundice (yellowing of the skin).

CF GENETICS

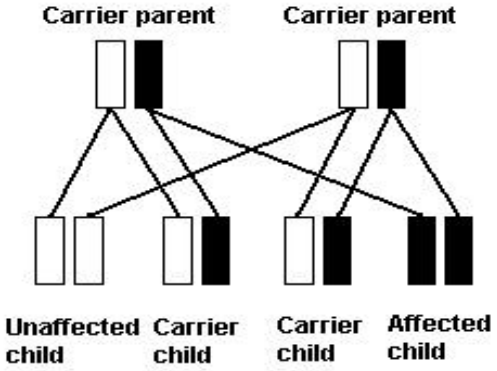
Inheriting CF

As outlined in **Box 2**, CF is a recessive genetic disorder affecting only those inheriting two faulty copies of the CFTR gene (one from each parent). People who inherit only one copy of the faulty gene (**carriers**) experience no harmful symptoms and are often completely unaware of their carrier status. Around 1 in 25 people in the UK are carriers of a faulty CFTR gene.

Different Mutations in the CFTR Gene

Over 800 hundred different faults (**mutations**) in the CFTR gene have now been identified. These different

BOX 2 INHERITANCE OF CF



Babies inherit two copies of most genes, one from each of their parents. In the case of CF, **both** CFTR genes have to be faulty in order for the individual to be affected by the disease. People inheriting one faulty and one normal gene are **not** affected by the disease, because the normal gene dominates over the faulty one (which is said to be recessive).

Although unaffected by CF themselves, individuals who have one normal and one faulty gene (**carriers**) run the risk of having children affected by CF. This can only happen if both parents are carriers of the faulty CFTR gene. As illustrated in the Figure above, 1 in 4 of children born to parents who are both carriers will have CF, 2 in 4 will be unaffected but will themselves be carriers, and 1 in 4 will be entirely unaffected (inherit 2 normal genes).

Roughly 1 in 25 Caucasians are carriers of a faulty CF gene but since both parents must be carriers to have a CF child only 1 in 625 couples will be at risk. Since only 1 in 4 children born to such couples will have the disease, this puts the overall risk at around 1 case of CF every 2,500 births (or a UK total of around 300 babies with CF every year).

mutations cause the CFTR protein to malfunction in different ways, affecting the severity of the symptoms suffered. Overall, there are five classes of mutations (**Table 1**), some of which prevent the CFTR protein being produced at all (Class I), others of which result in lower levels of production (Class V) or activity through some other mechanism. Some of these occur more frequently in some populations than others (see later).

ISSUES

Increased understanding of the molecular basis of CF holds out the promise of improved diagnostic tests and new treatments for the disease. Because it is one of the best understood genetic disorders, CF is often regarded as something of a test case for the thousands of other genetic conditions whose mysteries may soon be unravelled by the human genome project. However, even for a 'straightforward' disorder like CF, turning the new scientific knowledge into better treatments and tests raises a number of issues (discussed below).

TREATMENT ISSUES

While there is no cure for CF, there are a number of established treatments that alleviate the symptoms (see

TABLE 1 DIFFERENT CLASSES OF CF MUTATIONS

Mutation	Effect on CFTR protein
Class I	No production
Class II	Fails to reach cell surface
Class III	Incorrect regulation
Class IV	Partial activity
Class V	Reduced production

Box 3), including daily physiotherapy, treatment with antibiotics, enzyme supplements, etc. Developments in understanding the molecular basis of CF hold out the prospect of more effective treatment (Box 3). Approaches include gene therapy (GT) to introduce a healthy copy of the CFTR gene into the patient's cells and new drug strategies to repair the faulty protein, thin the mucous secretions, more effectively control bacterial infections, etc.

Of the various new approaches outlined in Box 3, most of the issues concern GT, regulated in the UK by the Gene Therapy Advisory Committee (GTAC). To date, GTAC have considered 6 protocols for CF, all of which involve the delivery of a healthy copy of the CFTR gene into the cells lining the lungs or nose. These have shown that GT can be used to temporarily normalise the passage of salts and water across epithelial cells. Development of these approaches to provide permanent expression of CFTR in the airways, or to allow for repeated administration of the healthy gene could result in significant improvements for CF sufferers in the alleviation of respiratory symptoms. However, if GT is to be an effective cure for CF, the healthy CFTR gene would have to be delivered to, and expressed in, all the affected tissues (not just airways but also pancreas and intestine).

One approach to achieving a permanent genetic change in epithelial cells would be to modify the stem cells from which they are derived. While these are not directly accessible, they could be modified by injecting the GT drug into the patient's blood stream. A second approach would be to correct the defect *in utero* and this has recently shown to be feasible using a viral vector to deliver the CFTR gene in a mouse model of CF. However, both of these approaches would increase the likelihood of affecting all the patient's cells, including the germ cells. This would raise ethical difficulties since any deleterious effects could be passed on to future generations. A recent report by GTAC on the potential use of GT *in utero* concluded that *ex vivo* GT (where cells are genetically modified outside the body) could be considered *in utero.* However, it noted that direct GT *in utero* was "*unlikely to be accepted for the foreseeable future"* due to ethical and safety issues.

BOX 3 CF TREATMENTS

Established Treatments - daily treatments may include:

- Chest physiotherapy, breathing exercises and regular physical exercise (to keep the lungs as free of mucous as possible thereby reducing infection);
- Mucous-thinning and airway-dilating drugs;
- Antibacterial drugs;
- Enzyme supplements (the pancreas is damaged at birth in almost all CF patients, so these replace the missing digestive enzymes);
- High fat and protein diets (to compensate for reduced food absorption);
- Lung transplants (as a last resort).

Potential New Treatments

Gene therapy (GT) - delivery and expression of a healthy copy of the CFTR gene into the patient's cells. GT trials for the treatment of respiratory CF symptoms have used either disabled adenoviruses (commonly found in the respiratory tract) or liposomes (tiny fat globules that fuse with membranes) to deliver the therapeutic gene. Trials so far suggest that both the efficiency of transfer of the CFTR gene and the persistence of its expression need to be improved. Research priorities include:

- Making the effects stronger and longer lasting;
- Overcoming the biological barriers (mucous, the body's natural defence mechanisms, etc.) to gene transfer;
- Making the changes permanent for example by modifying stem cells (precursors to the short-lived epithelial cells). Stem cells rather inaccessible, and may require the GT to be delivered in the patient's blood stream However, this would run the risk of altering non-target cells such as the germ-cells and this may adversely affect the health or development of the patient's future offspring;
- Giving GT at the earliest possible opportunity, since it is unlikely to be able to reverse established tissue damage. In the future it may be possible to correct CF *in utero*.

New Drug Treatments - among new approaches are:

- Protein repair therapy, where drugs are designed to 'correct' the faults in CFTR depending on the type of mutation. This approach has the advantage of being blood-borne and thus able to affect all the relevant cell types (intestine, lung, pancreas);
- Other drug approaches - better mucous-thinning drugs, anti-bacterials (including salt-resistant versions of the so-called defensins, found naturally in the lung but inactivated in the high salt concentrations of the CF lung) and anti-inflammatory drugs;
- Combination therapy - combining GT and drug therapy.

Other Treatment Issues

An additional issue concerning treatment for CF is the cost of prescription charges incurred by the need for continuous medication. The CF Research Trust has been campaigning for the introduction of legislation to exempt all adults with CF from such charges, and petitioned the Government on this issue in March 1999. It estimates that such a proposal would cost the Department of Health (DH) no more than £100,000 pa.

TESTING ISSUES

The UK already has one of the largest CF screening programmes of any country with tests for faulty CFTR genes being offered through the NHS's Regional Genetic Service. Current tests (**Box 4**) are designed to detect a limited number of the most common mutations, and have been targeted mainly at prospective parents from high-risk backgrounds (i.e. with a family history of CF). But recent advances mean that it is now possible to screen more people for more mutations, and this raises issues of who to test and when, the wider implications of screening, etc.

Who to Test and When?

In general, there are two main approaches to CF screening - testing prospective parents, or testing newborn babies. Prospective parents may be tested at the **pre-conceptual** stage, so that couples who both test positive for mutations have the widest possible range of options open to them. These include 'letting nature take its course', pre-natal diagnosis[1] with the option of terminating the pregnancy, avoiding pregnancy, changing partners, artificial insemination using a donor sperm or egg, and genetic testing of (*in vitro*) fertilised eggs to select those unaffected for implantation.

Ante-natal tests can be offered to parents after they have conceived, when they seek medical advice about the pregnancy. Carrier couples identified at this stage have fewer options open to them, but still face decisions over whether to consider pre-natal diagnosis and termination. Counselling is given to all couples in this position **before** they opt for pre-natal diagnosis since such procedures carry a risk (~1%) of foetal loss.

The main alternative to testing parents is to screen newborn babies (**neo-natal** screening). This can be achieved using genetic tests, or by other methods such as IRT tests (see Box 4). Some regional health authorities routinely do this at present, in order to identify babies with CF at the earliest possible stage, and thus allow treatment to start as soon as possible, although the long-term clinical benefits of early treatment have yet to be unequivocally demonstrated.

Pros and Cons of Screening Programmes

Current CF testing and referral strategies vary considerably from one Regional Health Authority to another. Bodies such as the CF Trust (a charity supporting CF sufferers and research into CF), consider that some form of CF carrier screening should be offered nationally in a reproductive context (i.e. in family planning and ante-natal clinics) and that neo-natal screening should be routine. This view is supported by recent recommendations on CF screening

[1] **This can be done in a number of ways such as amniocentesis or chorionic villus sampling (CVS, analysis of cells in the placenta).**

BOX 4 CF TESTS

Genetic Tests are designed to detect several of the most common disease-associated mutations in the CFTR gene (using a DNA amplification technique). Because the frequency with which the various mutations occur differs between ethnic groups, the proportion of carriers detected by genetic tests also varies. Commercial tests detect ~86% of carriers in Scotland, Wales and the North, and ~80% elsewhere. Detection rates among other ethnic groups vary from as high as 95% (Ashkenazi Jews) down to ~35% (Asian) of carriers. Additional tests may thus be conducted depending on an individual's ethnicity. While a positive result confirms someone as being a CF carrier, a 'negative' result cannot be 100% certain, since it is not practical to test for all known mutations. A carrier couple have a 1 in 4 chance of conceiving a baby with CF, and these odds are reduced to ~1 in 500 where only one of them has a detectable CF mutation, and to ~1 in 50,000 if neither test positive. Genetic tests are accompanied by counselling from specialist staff (**genetic counsellors**) associated with the regional testing centres.

Gene chips - tests based on 'gene chips' are currently being developed that will allow tens of thousands of mutations to be screened for in a single test (e.g. to screen an individual for all known CF mutations, rather than the testing for a handful of the most common ones). Such developments will result in quicker, cheaper and more accurate tests.

Other tests - non-genetic tests can also be used to screen newborn babies, and will detect those that have the disorder itself, but not healthy carriers of a CF mutation. One such method is the Immunoreactive Trypsin Test (IRT), which measures levels of IRT in the blood (babies with CF have 3 times higher levels than normal because of leakage of pancreatic secretions into the blood). Sweat tests, which detect elevated salt concentrations, are used to confirm CF diagnosis.

in a report to the NHS HTAP (Health and Technology Assessment Progamme[2], which also recommends screening for infertile men and sperm donors. The NHS Executive Screening Committee is reviewing this issue, and will consider a number of factors.

Aim of screening - pre-conceptual or ante-natal tests have the potential to reduce the overall number of babies born with CF. For this reason they are opposed by 'Pro-Life' groups that argue such tests will lead to a rise in the number of terminations (research suggests that many carrier couples who know their child will be born with CF opt for termination). Neo-natal screening avoids the issue of termination, but does not have the potential to reduce the number of CF births.

Cost - tests that reduce the number of babies born with CF may lower the overall costs of caring for CF sufferers (~£164,000 - £500,000 for lifetime treatment). But genetic tests are expensive, with ante-natal screening costing ~£46-53,000 per CF pregnancy detected. Neo-natal screening is cheaper (~£4,400-£6,400 per CF individual detected) largely because of the reduced need for counselling. This approach may offer benefits in terms of earlier treatment, but has little effect in reducing NHS costs for caring for CF sufferers. Looking ahead, the potential of 'gene chips' (Box 4) to test more people, more cheaply for more mutations will have implications for counselling resources.

Counselling - is given both before (where it informs decisions on whether to take a test or not) and after (to allow informed decisions on what to do) pre-conceptual or ante-natal tests. This is in accordance with DH guidelines for counselling in genetic screening that all individuals should have sufficient information to understand the proposal, be aware of any risks, and have time to decide and freedom to withdraw at any time. Thus, counselling represents a considerable part of the overall costs of testing, and any decision to increase the scale of tests would have significant resource implications. This was acknowledged in the report to HTAP, which noted that "*counselling is an important component of screening but unless an appropriate level is adopted the cost will be insupportable*" and recommended research into "*innovative methods for giving information on genetic screening*". As far as neo-natal screening is concerned, the report drew attention to the need for audit to ensure that parents give informed consent, since such tests may be conducted routinely on samples taken for other purposes. It also recommended "*more research on psychological and medical consequences for carrier detection in neo-natal screening*".

Other Testing Issues

Concerns over (commercial) genetic tests being supplied direct to the public led the Advisory Committee on Genetic Testing (ACGT) to draw up a Code of Practice in September 1997. This (*inter alia*) specifies who the tests can be supplied to (people over 16), what type of tests may be supplied (tests for inherited recessive disorders such as CF) as well as providing guidance on confidentiality, information supplied with the tests and the involvement of medical practitioners. As far as NHS involvement is concerned, the Genetic Interest Group (an umbrella organisation for genetic disorders) is campaigning for a national strategy for genetic disease services to eliminate regional variation in the quality of care. This and other issues concerning genetic testing will be dealt with in a forthcoming POST Report on Human Genomics.

[2] **Murray J, Cuckle H, Littlewood J, Taylor G & Hewison J Screening for CF, Health Technology Assessment, 1999 (in press).**

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