

cf today

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for a
brighter
tomorrow

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The primary purpose of *CF Today* is to provide for its readers a reliable source of medical, research and other information relevant to Cystic Fibrosis and to play a supportive role for CF families. Opinions expressed in articles do not necessarily express the official policy of the Cystic Fibrosis Trust. The editor reserves the right to edit and otherwise alter articles or letters submitted to the magazine for publication.

Some pictures used in this publication may be posed by models or taken from library images.

The contents of CF Today have been written to assist people with CF and their medical advisers. Medical information included in this publication is not intended to replace any advice you may receive from your doctor or CF multidisciplinary team and it is important that you seek medical advice whenever considering a change of treatment regimen.

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Cystic Fibrosis Trust Helplines

Our Support Service has three Helplines offering the following services:

For information and advice on Disability Living Allowance (DLA), how to apply and advice on completing the DLA form –

 **Benefits Advice**
0845 859 1010
From 1 April: 0300 373 1010

For a *confidential* service that enables anyone to obtain information, advice and support on any aspect of Cystic Fibrosis –

 **CF Helpline**
0845 859 1000
From 1 April: 0300 373 1000

For information and advice on how to access small grants from the Cystic Fibrosis Trust and other organisations –

 **Welfare Grants**
0845 859 1020
From 1 April: 0300 373 1020

Our Helplines operate from 9am – 5pm weekdays. An answer machine is available during busy periods and outside these hours.

You can also access our website www.cftrust.org.uk to find out more about CF Trust Helplines and to download various forms and factsheets relating to these services.

Editorial

Dear Friends,

Firstly, if it's not too late, may I wish you all a happy and healthy New Year.

Many of you will have been to the meeting at Imperial College in London recently to have an update on how the gene therapy research is going. The banner headlines from the pilot study are that overall the treatment appears to be safe and there are some important indications that significant, positive changes have occurred in some of the patients.

One of the reasons for the pilot study is to get the dose right. Some adjustments in this area are being considered, as a lower dose than the one (20ml) given to some patients in the pilot may be appropriate. For more information on gene therapy, please see the article on page 14.

We are still extremely busy addressing all aspects of clinical care, to ensure that everyone with CF gets the best possible NHS care, irrespective of where they live. Our programme of peer reviews is proceeding apace. Nearly 40 Specialist CF Centres and 30 Clinics have been peer reviewed so far. This year we will be peer reviewing six or seven more CF Centres and over 30 more Clinics. This is a detailed and time-consuming process which to date has resulted in an additional £14 million plus for CF care, via the NHS, without you having to shake a single tin! About two thirds of the Centres we have reviewed have reported improved resources, including better inpatient facilities, improved outpatient clinics and increased staffing. This is very encouraging, but there is a lot more to be done, not least to revisit the one third of Centres who have seen little or no improvement.

The CF Registry (Port CF) goes from strength to strength. We now have over 8,500 patients registered and full data on over 6,000. It is encouraging that the median predicted survival is now 38.8 years, and likely to improve further year on year.



We are also pleased that our training grants, to ensure there are enough CF consultants to look after the ever increasing number of adults with CF, continue to prove popular and successful. Two more trainees have just been appointed, one at Papworth Hospital in Cambridge, and another at Wythenshawe Hospital in Manchester. Dr Felicity Perrin, who is coming to the end of her training at the Royal Brompton Hospital in London, has just been appointed as the second CF consultant for the adult service at King's College Hospital in London.

Finally, some personal news. I will be retiring in 2010. I will by then be 64 and I want to hand over whilst I am still 'firing on all cylinders'. I also want to free up some time to help my daughter, who herself has a very serious medical condition, look after her baby, expected in February. I will, of course, always be a very loyal ambassador for the Cystic Fibrosis Trust and will help in any way I can, in a different capacity. As I will not be retiring until August or thereabouts, it will be business as usual until then. No long goodbyes!

Rosie Barnes

Rosie Barnes
Chief Executive

CF Week 17-23 May!

This year's CF Week will be held on 17–23 May. The focus of this week will be to launch our brand new fundraiser The Big Cake Bake.

This is designed with simplicity and fun in mind. Gather friends, family and colleagues, put the kettle on, get creative and get baking! Alternatively you can organise a collection, participate in an event or organise your own. For more details please visit www.cftrust.org.uk or contact our Events Team on 0845 859 1100 or events@cftrust.org.uk who can provide you with The Big Cake Bake fundraising pack.

The next editions of *CF Today* and *Focus on Fundraising* will be published a bit earlier – towards the end of April – so we can highlight all of the great activities and fundraising events taking place. Put it in your diaries now!



Prescription Charges Latest

Recommendations on how to implement the Government's pledge to phase out prescription charges for all those with long-term conditions in England have been submitted to the Department of Health by Professor Ian Gilmore, President of the Royal College of Physicians. At the time of going to press, the Department of Health was expected to respond to the report in the new year. Keep an eye on our website for updates.

New Hope for Lung Transplants

You may have read at the end of last year about a new method to 'recondition' lungs for organ donation that had been deemed unsuitable for transplant. James Finlayson, a 24-year-old with Cystic Fibrosis received a lung transplant using the method, which involves placing the organs in a chamber connected to a heart bypass machine, and treating them with a nutrient-rich solution that allows the damaged cells to begin repairing themselves.

It is hoped that the method may significantly improve the UK's shortfall in availability of suitable organs for transplant, and transplant centres across the UK are expected to begin implementing the procedure this year.

An article about the research, which was led by Professor Andrew Fisher at the University of Newcastle and was part funded by the CF Trust, was featured in *The Times* and can be viewed online at www.timesonline.co.uk/tol/news/uk/health/article6958120.ece.

Improvements in Understanding of the Basic Defect



Dr David Sheppard monitoring pH levels in tests

Also in December, a research study funded by the CF Trust into understanding the basic defect in CF was published by the *Journal of Biological Chemistry*. This project was led by Dr Jeng-Haur Chen, now of the University of Iowa and overseen by Dr David Sheppard at the University of Bristol. It investigated how the activity of CFTR (Cystic Fibrosis Transmembrane Regulator – the protein that controls the movement of salt through the cells in the body) is regulated by how acid or alkali (the pH level) the cells are.

The relationship between CFTR and pH levels was not known, but Dr Chen found that it is the actual pH level that controls the CFTR and therefore the movement of salt and bicarbonate in the body – the basic fault in Cystic Fibrosis. An acidic pH (less than 7.0) tells the body to move salts and an alkaline pH (more than 7.0) slows it down.

"By targeting the root cause of the disease, rather than the symptoms, new drug therapies for CF might stop disease progression and prevent the decline in health of individuals living with CF" said Dr Sheppard.

Charity of the Year – could you help?

The Cystic Fibrosis Trust has been shortlisted to become Charity of the Year 2010 for Network Rail. Voting starts on February 8 and will run for four weeks, so if you know anyone who works for the company, please contact them and ask if they would consider voting for the CF Trust. For more info contact Gemma – gwoodward@cftrust.org.uk. Fingers crossed!



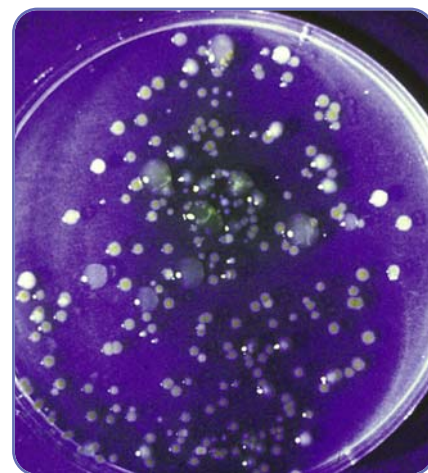
Image: © Vladimir Voronin – Fotolia.com

Drug Developments

The antibiotic aztreonam lysine (trade name Cayston), developed by Gilead Pharmaceuticals UK Ltd to treat chronic *Pseudomonas aeruginosa* infection in adults with Cystic Fibrosis, has been granted conditional marketing authorization in the UK. Conditional marketing authorizations are granted to products whose availability would result in an unmet and significant public health benefit, but which must undergo further trials in order to be fully authorized – in the case of Cayston meaning full marketing approval will be granted

providing a phase III study is conducted to compare its efficiency to the antibiotic tobramycin, which is also effective against *Pseudomonas*.

At the time of going to press, the drug, which will be delivered via a nebuliser, was expected to be available for prescription in the first quarter of 2010. Professor Stuart Elborn, Chair of the Cystic Fibrosis Trust Research Advisory Committee, described the drug as “an important addition to the fight against infection in people with Cystic Fibrosis.”



The fight against *Pseudomonas* continues

Got Our Number?

From 1st April 2010, we are replacing our current 0845 numbers with the new 0300 numbers specifically designated for charities. Calls will cost the same as calls to our current 0845 numbers – the same as a local rate

call when made from a BT landline. Here are a few of the key numbers (you will still be able to contact the main switchboard on 020 8464 7211):

	Until 1 April	After 1 April
Cystic Fibrosis Helpline	0845 859 1000	0300 373 1000
CF Welfare Grants Helpline	0845 859 1020	0300 373 1020
CF Benefits Helpline	0845 859 1010	0300 373 1010
Events line	0845 859 1100	0300 373 1100
Donations line	0845 859 2040	0300 373 1040

Living with Cystic Fibrosis – Emotional difficulties and how to deal with them

Living with any long-term health condition can be a challenge and Cystic Fibrosis is of course no exception. Alongside the physical effects of CF and the impact upon life of the treatment regimes, CF can also have an emotional impact. As a result many CF Centres now have their own psychologists and social workers. This article describes some of the emotional aspects of living with CF as seen by two Consultant Clinical Psychologists, Dr Mandy Bryon of Great Ormond Street Hospital, London and Dr Helen Oxley of Wythenshawe Hospital, Manchester, who have worked with people with CF and their families for many years.

Emotional issues for children with Cystic Fibrosis

Years ago the prognosis for children diagnosed with CF was poor and many children lived their lives feeling very sick, with little opportunity to participate in typical everyday activities. It was assumed that those children would be feeling very depressed and anxious, though in fact properly conducted research showed that children with CF did not have higher incidence of emotional dysfunction than those without Cystic Fibrosis. These days the prognosis for a child diagnosed with CF is much more positive and most children with CF will feel fit and well. Of course, nowadays children with CF and their parents are more likely to have regular

access to a psychologist or social worker as part of their routine care, which means that occasional emotional upsets can be identified quickly and even prevented. However, it is still the case that CF requires daily time-consuming treatment regimes which can take their toll on children and the rest of the family.

"One of the most pervasive emotional difficulties facing the school age child is a feeling of difference compared to peers."

Having CF can affect a child's self-concept and one of the most pervasive emotional difficulties facing the school age child is a feeling of difference compared to peers. Children will go to great lengths to minimise observable differences between themselves and peers and so for those with CF this can mean failing to conduct necessary treatments and being reluctant to let anyone know their diagnosis. One of the most common emotional issues for young children is to learn their diagnosis, understand how CF affects them and to ensure they have an appropriate perspective on living with Cystic Fibrosis. It is important that children with CF see themselves as 'a normal child who happens to have CF,' rather than 'a child with CF who is trying to be normal.'

By and large children with CF cope exceedingly well with managing their condition and getting the balance right between living a normal life and fitting treatment into their daily routine. On occasions children with CF do develop more entrenched emotional problems; this can be as a result of increased understanding of their condition and feeling overwhelmed by what the future may hold, but it can also stem from unrelated external influences. Children and adolescents are not always good at

being able to say how they are feeling mostly because they have never experienced these emotions before or they are too young to put feelings into words accurately. It is left to those around them – parents and other adults – to be alert to changes in behaviour which may be an indication of emotional disturbance. Some behaviours to look out for are:

- Showing declining performance in school
- Losing interest in things once enjoyed
- Experiencing unexplained changes in sleeping or eating patterns
- Avoiding friends or family and wanting to be alone all the time
- Daydreaming too much and not completing tasks

If a child or adolescent is able to express how they are feeling, then commonly reported concerns are:

- Feeling sad and hopeless for no reason, and these feelings do not go away
- Feeling very angry most of the time and crying a lot or overreacting to things
- Feeling worthless or guilty often
- Feeling anxious or worried often
- Being unable to get over a loss or death of someone (or a pet)
- Being extremely fearful or having unexplained fears
- Being constantly concerned about physical problems or physical appearance
- Being frightened that his or her mind either is controlled or is out of control

Emotional issues for adults with Cystic Fibrosis

Adults with CF generally have many years experience of coping with CF and the demands it can put upon them, their families, social lives, education or jobs. Over time, coping strategies are developed, and adults with CF generally manage what CF has to throw at them well. Sometimes however, the challenges can feel too great and difficult emotions arise. Many things may bring about a 'bad patch' with CF, emotionally



"Often stressful times will pass with good support and good coping strategies."

speaking. Common triggers include:

- Changes in health
- New symptoms or complications of CF
- When CF affects friendships, relationships or family life
- When CF affects decisions about education, career plans, or having a family
- Spending more time at or in hospital
- Increased treatments and the effect on life balance / quality of life
- Loss of friends, family, or peers with CF

Common emotional reactions to CF in adults include:

- Feelings of anger or frustration at times
- Feelings of sadness or worry
- Feelings of 'Why me?'
- Feeling irritable
- Feeling overwhelmed or confused
- Feeling different, or bad about yourself

Dealing with difficult emotions or stress can also lead to symptoms such as:

- Changes to sleep patterns
- Tension or anxiety
- Being short tempered and snappy
- Changes in appetite or eating patterns
- Physical symptoms, such as aches and pains, stomach upsets, changes to breathing pattern

Often stressful times will pass with good support and good coping strategies. If difficulties persist, problems such as depression or anxiety disorders (eg. panic attacks, excessive worrying, obsessional behaviours) can sometimes develop. The rate of depression and anxiety in people with CF is not yet clear and a large study is now taking place worldwide to tell us this. However, in people with other long-term illnesses, depression is known to be quite common, with one in five experiencing it at some time in their life.

Dealing with difficult emotions for yourself or your child with Cystic Fibrosis

If living with Cystic Fibrosis is proving difficult emotionally, either for yourself

or your child / children with CF, then it may be important to seek some help with this.

Often just talking more openly to friends or family, or to others with CF through forums etc, can help a lot. Getting more support from someone who will at least try to understand, can help see you through bad patches.

Children are not always willing to talk, even to their parents – it may take several 'nudges' before they feel confident enough to disclose their thoughts. It is important that children get the message that someone is willing to listen if they want to tell, and that anything they say will be treated with respect. Sometimes it can be helpful telling children that worries are often worse if they are kept to themselves and if they share them, then they get a better chance of solving the problem.

If more help is needed, there is lots of advice available on how to cope with stress and other common psychological issues (see some of the suggestions on the right). Other leaflets may be available in your CF Centre or Clinic or GP surgery. If you need to seek more specialist help this may be available in your CF Centre – many now have a social worker or psychologist who will have a good understanding of how CF can affect life. If your Clinic does not have these staff, you will need to go to your GP who should be able to refer you or your child for appropriate help.

For some problems, such as moderate or severe depression, a combination of suitable medication (anti-depressants) and a form of psychological therapy called cognitive behaviour therapy (CBT) is the recommended treatment approach, and should be made available if needed.

Emotional reactions to living with CF can range from a few bad days, to more significant problems that last much longer. On the other side of the coin, many adults with CF say that living with its challenges has made them stronger as



people. Certainly the impressive coping strategies, humour and resilience shown by people with CF are often noted by those in close contact. Either way, the impact of CF upon emotions is now very well-recognised, so don't feel embarrassed or reluctant to seek help for yourself or your child if this is needed at any time.

Some suggestions for further information/advice:

- Manage your mind by Gillian Butler & Tony Hope. Oxford University Press (A useful book for adults, giving good advice on dealing with many different psychological issues)
- www.patient.co.uk (This website has information leaflets on anxiety and depression, amongst many other topics)
- *CF Today* Autumn 2006 Cognitive behavioural therapy (www.cftrust.org.uk/aboutcf/publications/cftoday/cftoday_backissues)

The CF Trust website also has several forums for young people and adults with CF, and parents and carers, which can be accessed from the homepage www.cftrust.org.uk.

Reference:

Prevalence and impact of depression in cystic fibrosis. Quittner A L et al. *Current Opinion in Pulmonary Medicine*. 2008 14:582-588.

Images: Kayleigh Bluck

Ask the Expert

In this edition of Ask the Expert, we answer two questions on 'mild' or 'atypical' CF, offer advice on what to do when CF is suspected after a negative screening result, examine the cause of low parathyroid levels and discuss whether epilepsy can be linked to Cystic Fibrosis.

Atypical CF

Q My 20-year-old son was diagnosed with bronchiectasis a few years ago, which has been resistant to all antibiotics including intravenously for one week. He has now been told that he has one CF gene and one normal gene. I thought this meant he would be a carrier and not have CF, but his doctor seems to think it is relevant and may be a rare type of Cystic Fibrosis. Sweat test was normal, he doesn't have digestive problems and there is no family history of CF. Is it possible to have a variant of CF with just one abnormal CF gene? Might his fertility be affected?

A The key to your question is in the second sentence, "he has now been told that he has one CF gene and one normal gene". This is often the interpretation that patients and some health professionals make but what the genetics lab actually said was "there is one abnormal (CF) gene and we have not been able to recognise an abnormality on the other gene". There are literally hundreds of abnormalities that have been recognised that cause the CF gene to not work properly and it is impossible to be completely sure that the CF gene is 'normal'. Some of these gene changes are actually outside the CF gene and affect the efficiency with which the CF gene works.

It is possible therefore that your son has an as yet unrecognised, gene change which is affecting his other CF gene. The clinical features that you describe do not preclude this. Often these unusual gene changes are associated with some residual function of the CF gene and people with this situation do not present with the classical picture of Cystic Fibrosis. This condition is often called 'atypical CF' and certainly the 'normal' sweat test and lack of digestive symptoms do not preclude this diagnosis. The Vas Deferens (the sperm-carrying tube connecting the testes with the urethra) is particularly sensitive to changes in CF gene function and absence of the Vas Deferens (causing infertility) is a common feature of atypical CF in men. Examination of the Vas Deferens by an experienced urologist can sometimes be helpful, but obviously this needs to be done sensitively. There are other investigations that measure salt transport and these can also help to clarify a diagnosis of atypical CF; these are generally available through experienced CF Centres.

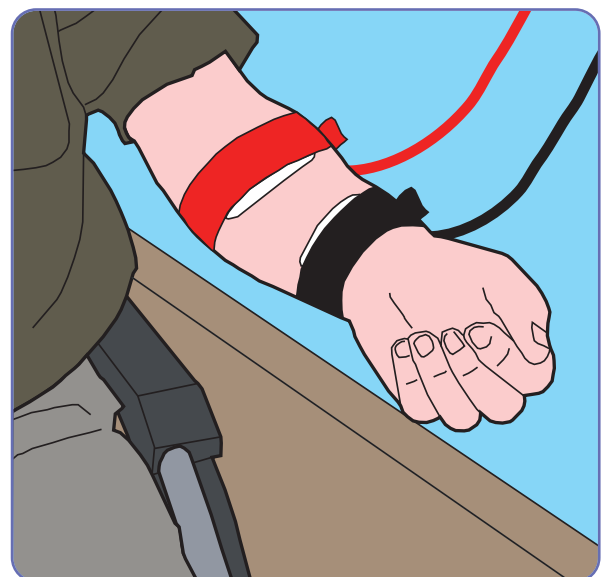
In summary, the finding of bronchiectasis and one CF gene change in a 20-year-old man would be consistent with a diagnosis of atypical Cystic Fibrosis. It is important that extensive DNA analysis is undertaken to look for unusual CF-causing gene changes and that your son has opportunity to be reviewed in a CF Centre with expertise in assessing these diagnostic issues.

Look out for a longer article on atypical CF in the next edition of *CF Today*.

Negative screening

Q My 18-month-old son has had chest problems more or less from birth and although he tested negative for CF at his newborn screening, I am slightly concerned. My sister had Cystic Fibrosis and I recently tested my son's sweat to find it does taste noticeably salty – more so than his sibling. Do you think I am being paranoid or is there a chance that the screening might not have picked CF up?

A For the last two years, all newborns in the UK have been screened for Cystic Fibrosis. If a child has any symptoms which could be connected to CF following a negative result then it is advisable to ask GP for a referral for a sweat test. We have a Sweat Test factsheet on the website under publications www.cftrust.org.uk/aboutcf/publications/



Sweat Test

The fact that your sister had CF means there is an increased risk of your son being a carrier. If the sweat test was not conclusive it may be possible to follow up with genetic testing.

Parathyroid hormone

Q My son has results showing he has low parathyroid hormone levels. Is this caused by treatment of CF or part of the disease? His vitamin D levels are low and he also has osteopenia (low bone mineral density).

A Vitamin D's main action is to allow calcium to move from the gut into the bloodstream. If vitamin D levels are low, then calcium cannot move from the gut into the blood – this can then lead to poor bone development. If the blood calcium levels are low, the parathyroid gland releases parathyroid hormone, which in turn allows calcium to be taken out of the bones to maintain a safe blood calcium level.

Therefore, the parathyroid hormone level is usually HIGH when the vitamin D level is LOW. When this is the case, the patient should see their CF doctor and CF specialist dietician to discuss ways of improving their vitamin D levels. This is often through a combination of increased dietary supplementation with vitamin D and calcium (and sometimes increased sunlight exposure as this leads to vitamin D production in the skin – patients must never get burnt though!).

Epilepsy

Q My 18-year-old granddaughter has CF and recently suffered an epileptic fit. She was observed for four hours in hospital and sent home – the doctors said that she would have to suffer two fits before any tests would be done. I would like to know if there is any connection between CF and epilepsy.

A (Answered by CF Trust Helpline) I have never heard of anyone with CF having epilepsy. Children and adults with Cystic Fibrosis can have any other condition that affects the general population.

I suggest your granddaughter contact her specialist CF team who can refer her for investigation. It might be worth you checking out the National Society for Epilepsy (NSE) website www.epilepsysociety.org.uk – they have information about adult onset epilepsy.

Mild CF?

Q My son is 32. From the age of six months he suffered from heavy chesty colds. From about five years old, most colds would turn into chest

infections and if left untreated would turn into pneumonia. At the age of 11 and still suffering from repeated chest infections my GP sent him to the hospital for tests. He is not asthmatic and after numerous immune system tests he was finally given the sweat test and repeatedly tested positive. We were told that he did not have Cystic Fibrosis, but I don't know how they came to that conclusion other than the fact that he was a strapping lad. As he grew into his teens he continued to have chest infections and some very nasty bouts of pneumonia when he was at university. Through his twenties he had less infections but he does complain now of painful IBS type symptoms. My question is: can you have a mild version of CF and could this be the cause of his digestion problems?

A It is possible to have a very mild form of CF and for adults to be diagnosed at any age. You do not say if your son had any genetic tests – this is what I would have expected after having positive sweat tests. Sometimes they may only find one copy of the CF gene and not two; they would then treat the symptoms.

Our experts for this issue were:

Dr Charlie Haworth, Consultant Respiratory Physician, Papworth Hospital, Cambridge

Dr Jim Littlewood, Chairman, Cystic Fibrosis Trust

Dr Kevin Southern, Honorary Consultant in Paediatric Respiratory Medicine, Alder Hey Childrens' Hospital, Liverpool

Cystic Fibrosis Trust Helpline

Ask the Expert is not intended to replace expert advice from your healthcare providers. It is very important that you always seek the advice of your own consultant, GP or other qualified health professional.

If you have a question you would like to Ask the Expert either visit our website www.cftrust.org.uk or send by post your question about treatment, medication, nutrition or any other aspect of living with CF to:

CF Today
Cystic Fibrosis Trust
11 London Road
Bromley
Kent BR1 1BY

Although your letter may appear on the website or in our magazine, your personal details will remain confidential. Your questions will be dealt with by a panel of medical experts who specialise in different areas of Cystic Fibrosis.

Safe Use of Antibiotics

Before antibiotics and other drugs were used regularly and when necessary intensively to treat people with Cystic Fibrosis, life expectancy and indeed quality of life was very much poorer than it is now. We now know that both length and quality of life can be increased and improved markedly by the use of effective drugs.

The median predicted survival for someone with Cystic Fibrosis is now 38 years (meaning half the people with CF will live to a greater age than 38 – see next page for more on this) so considerable progress is being made. However this increased life expectancy brings its own challenges. We need to ensure that the drugs used are as safe as possible to minimise the likelihood of short-term and long-term side effects, whilst keeping the infections that invade the lungs of someone with Cystic Fibrosis under control.

Antibiotics and other drugs used in the treatment of Cystic Fibrosis are given in a variety of ways, including orally, in tablet or liquid form, via a nebuliser, or intravenously.

Oral antibiotics have been very beneficial for those with Cystic Fibrosis. As with any drug, some people can have an allergic reaction to them and some drugs (co-amoxiclav in liquid form and tetracyclines in children under 12) can cause staining of the teeth. Overall, though, few studies have shown any serious adverse reaction to oral antibiotics.

Nebulised antibiotics have the advantage of getting straight into the lungs where the infection is located, and because they are only minimally absorbed into the bloodstream and therefore into the system, they are far less likely to cause some of the problems that can occur with intravenous antibiotics (IVs).

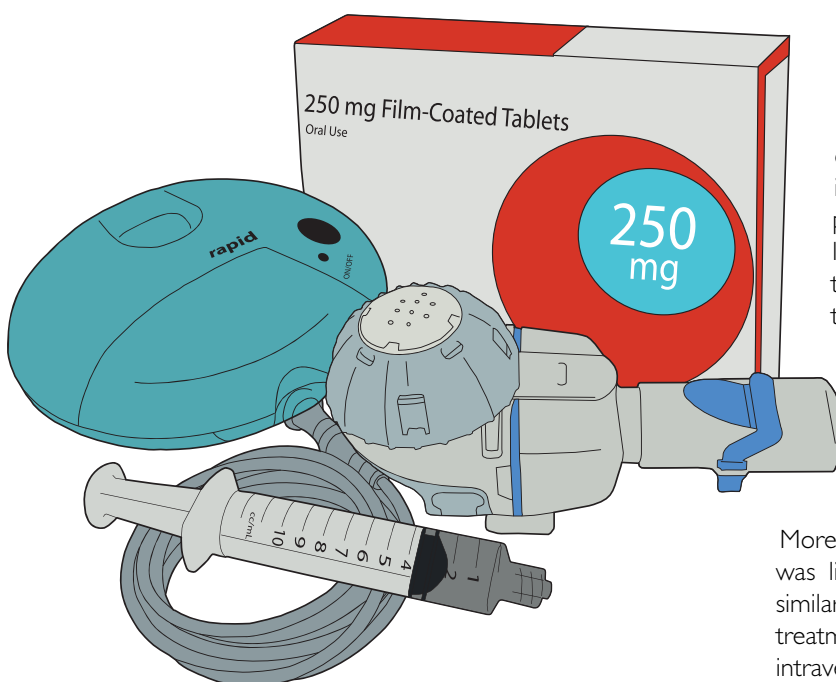
Intravenous drugs are extremely effective and therefore a valuable tool in the control of Cystic Fibrosis infections. However, as the drug goes straight into the bloodstream, it gets into the body's system where it has the potential to affect other organs than the one targeted. In this way, it has the potential to do harm as well as good.

Problems which are known to arise include ototoxicity (hearing loss) or nephrotoxicity (kidney damage). These problems are particularly associated with a certain group of antibiotics called aminoglycosides, three of which are particularly relevant to Cystic Fibrosis as they are effective in tackling *Pseudomonas aeruginosa*. These three are amikacin, tobramycin and gentamicin, which go under various brand names. It is important to note that given carefully, these drugs can be very helpful in the control of Cystic Fibrosis, but if given without adequate monitoring, serious problems can arise.

These are far more likely to occur if the drug is given intravenously, when it gets into the system and can affect other organs such as the inner ear and the kidneys. There is no evidence that serious or long-term damage occurs if the drug is given via a nebuliser, where very little is likely to get into the system as a whole.

Side effects are mostly dose-related and are also likely to be related to the length and number of courses of intravenous antibiotics. Research has indicated that intravenous gentamicin is of particular concern, and is known to cause hearing loss and renal problems in some people. It is therefore recommended that intravenous tobramycin is used, which is more active against *Pseudomonas aeruginosa* and appears to be considerably safer. For many years tobramycin was only licensed for intravenous use, although that preparation has been used effectively in nebulised form for many years for those with Cystic Fibrosis in the UK.

More recently a particular brand of tobramycin, TOBI, was licensed for nebulised use; also more recently a similar preparation Bramitob. Tobramycin is a valuable treatment and will be prescribed in both nebulised and intravenous form as needed.



Gentamicin should be avoided wherever possible for intravenous use and whilst inhaled gentamicin is less likely to cause problems, as other inhaled drugs including aminoglycosides which are licensed and known to be safer are available, these are recommended. These are colistin (Colomycin or Promixin) and tobramycin solution for inhalation (TOBI and Bramitob).

As with all drug regimes, the interaction between drugs must always be considered, and usually it is recommended that nebulised drugs are discontinued for the period that intravenous drugs are given.

For nebulised drugs, it is recommended that the first dose is given in hospital on a supervised basis. Intravenous antibiotics may be given in hospital or at home, but tobramycin levels should be monitored regularly to ensure the drug is not reaching toxic levels in the bloodstream, irrespective of the patient's location.

To summarise, there are four key points to bear in mind:

1. Antibiotics are invaluable in treating those with Cystic Fibrosis to ensure a longer and better quality life.
2. There are no real safety concerns in relation to antibiotics given orally.

3. There is little evidence that nebulised antibiotics cause serious long-term problems.

4. Whilst a group of drugs called aminoglycosides are very effective in treating *Pseudomonas aeruginosa*, one of them, gentamicin, is associated with serious long-term adverse side effects, especially when given intravenously. As there are safer, effective alternatives, gentamicin is better avoided unless other drugs have been tried and have proved to be ineffective.

Details of intravenous aminoglycoside administration can be found in the Cystic Fibrosis Trust's consensus document, *Antibiotic Treatment for Cystic Fibrosis. Third Edition. May 2009*, which is available to download from www.cftrust.org.uk/aboutcf/publications/consensusdoc. The recommendation at bullet point five of section 6.7 of this document states that "tobramycin is the aminoglycoside of choice and gentamicin should be avoided."

If you have any queries about the information in this article or concerns about the use of gentamicin, we suggest that you speak to members of the CF team at your local Specialist CF Centre – a list can be found on www.cftrust.org.uk/aboutcf/cfcare/ukcfcentres.

Median Predicted Survival

As you may recall reading recently, the median predicted survival for CF (the age to which half of people with CF can currently expect to survive) is continuing to rise. In the last *CF Today*, we reported that median predicted survival was 35 years – this was based on the 2007 data in our CF Registry. Since then, we have analysed the data from 2008. The amount of data we have in the Registry is increasing all the time as further Centres and Clinics across the UK submit information about their patients. For instance, we now know that there are over 8,500 people with CF in the UK and there may be around another 1,000 or so for whom we have no data.

Taking this additional information into account, we now estimate that median predicted survival stands at 38 years. This does not mean that survival has jumped by three years in such a short space of time, but that the increasing data we have has allowed us to make a more accurate prediction. It is important to remember however that statistics are just that – every person with CF is an individual and no two people with CF have the same disease course. But this is of course good news, and we have every reason to believe that with improvements in care and treatment and our ever-increasing knowledge of CF, the outlook for everyone with Cystic Fibrosis will continue to improve.

Correction

The article on adherence to treatment in the autumn 09 edition of *CF Today* was written by Dr Bernadette Donaghy and Kate Lamballe, of James Cook University Hospital, Middlesbrough.

The CF Microbiology Consortium: History and Legacy

The Cystic Fibrosis Microbiology Consortium was a research project funded for three years, which aimed to improve the social and economic inclusion of children and young adults with Cystic Fibrosis by increasing understanding and improving treatment of 'superbugs' such as MRSA and Burkholderia and serious lung infections. Bringing together scientists and clinicians with internationally-recognised experience of CF lung disease and complementary expertise, the Consortium, led by Professor Govan of the University of Edinburgh's Centre for Infectious Diseases, made great strides in our understanding of CF microbiology. Although funding for the Consortium ceased in October 2008, its legacy lives on, as Professor John Govan here explains.

Funded by grants from the Big Lottery Fund (BLF) and the Cystic Fibrosis Trust, the Consortium's research focused on three major areas that are of imminent and important clinical relevance to people with CF:

1. Early and rapid diagnosis of pulmonary infections to enable rapid implementation of appropriate antibiotic therapies and infection control procedures.
2. Bacterial genomics uses new research approaches derived from knowledge of a bacterium's genome and its DNA. The Consortium used these new technologies to identify and characterize genes and gene clusters responsible for virulence and transmission of the major CF pathogens.
3. Characterization of the mechanisms of resistance to antimicrobial agents which are evident in the major CF pathogens, and the development of novel antimicrobials and / or antimicrobial combinations.

The overall aim of the Consortium was to improve the speed and accuracy of diagnosis and treatment of respiratory infections in people with Cystic Fibrosis, along with gaining a better understanding of how bacteria work, in order to identify alternative approaches to developing new therapies. The Consortium also hoped to improve quality of life and reduce the need for patient segregation and the resulting feeling of isolation and exclusion that are associated with current measures to reduce respiratory infections.

"The Consortium aimed to gain a better understanding of how bacteria work."

The CF Trust applied to the Big Lottery Fund and were given funding of £510,000, the largest research grant awarded by the BLF (and more than we had asked for). The CF Trust also gave some additional support and the Consortium recruited four PhD candidates to work with experienced CF researchers at the Universities of Cardiff, Edinburgh, Liverpool and Queen's University, Belfast and a senior post-doctoral researcher at Edinburgh, who acted as co-ordinator. Although working on individual projects, Consortium members met regularly to report progress and draw on each other's expertise under the umbrella

of the Consortium. Associate members were also encouraged to participate and provide specialist skills. Information was shared between Consortium members and the general public by the creation of a Consortium website developed by Alan Brown of the Consortium, which can still be accessed at www.cfmicrobiology.org.uk.



John Govan with Dr Cathy Doherty

© Peter Tuffy, The University of Edinburgh

Persuading the BLF to fund this highly novel enterprise was a challenge matched by the need to comply with the bureaucratic and regulatory requirements of four universities. However, the exercise proved hugely successful, as is summarised below:

- Members of the UK CF Microbiology Consortium published their research in 21 scientific publications with a further eight papers under revision or in preparation – a major contribution to CF microbiological research, and improved patient care.
- A detailed report on the Consortium was submitted to the Big Lottery Fund and to the CF Trust's Research Advisory Committee in 2009. Further information and updates can be found at the consortium's website: www.cfmicrobiology.org.uk
- The Consortium offers a potential model for the CF Trust to support further groundbreaking and PhD-led microbiological research. A senior executive of the Medical Research Council who attended the final Consortium meeting at the CF Trust headquarters in Bromley in 2008 was highly impressed with the structure of the Consortium as model for training of young researchers in interdisciplinary research focused on patient care.
- At a time when research funding is limited, the Consortium has been highly influential in attracting CF-related funding from alternative sources.
- In addition to the successful presentations by the PhD students to the Consortium and elsewhere, two of the students won prestigious young researcher awards at international meetings:
 - Jo Fothergill at the 2007 European Cystic Fibrosis Conference in Prague.
 - Josefin Bartholdson at the 2008 International Endotoxin Meeting in Edinburgh.
- All PhD students successfully completed their theses on time and details of their present positions are available.

Although funding has now ceased, we hope that the advances made by the Microbiology Consortium will continue to aid the understanding and treatment of CF respiratory infections, and allow people with CF, their carers and CF teams to tackle these infections with greater efficiency, and fewer constrictions.

Know Your Onions (and enjoy them!)



We often receive queries from people with CF and concerned relatives about the infection risks posed by the environment, for example from animals, water or foodstuffs. We've received several queries recently about a possible link between onions and the bacteria *Burkholderia cepacia*, which can cause serious problems for people with Cystic Fibrosis (and for onions!). Here John Govan, Emeritus Professor in Microbial Pathogenicity at the University of Edinburgh, clears up some of the confusion surrounding whether onions can be safely included in the CF diet.

'*Burkholderia cepacia*' is named after the plant pathologist Walter Burkholder, who in 1950 showed that this soil bacterium was responsible for a disease in commercially-grown onion bulbs known as sour skin, or soft rot. This brief introduction highlights the versatility of these extraordinary bacteria, since it is difficult to imagine a more formidable host for bacterial disease than the eye-watering onion.

Following Burkholder's discovery, *B. cepacia* remained relatively unknown until the 1980s when it emerged in people with CF as a cause of serious lung infections. These infections were unpredictable in outcome, difficult to treat because of the organism's natural resistance to antibiotics and, unlike most other bacterial pathogens, could be transferred from patient-to-patient through social contact. Oddly, at the same time, strains of *Burkholderia* were also creating considerable interest in agriculture as highly effective biopesticides to control fungal infections in crops.

In the last two decades, microbiologists have learned a great deal about this fascinating (though not to the CF community!) group of organisms. Today, the term *B. cepacia* complex (Bcc) describes a group of 17 closely-related bacterial species. Accurate laboratory identification of the group, particularly at species level, is challenging. Two species, *B. cenocepacia* and *B. multivorans* account for over 80% of all CF *Burkholderia* isolates; the former is also the species most closely associated with the life-threatening outcome, known as "cepacia syndrome". Infection control measures (including segregation of infected patients), both inside and outside of hospitals, have dramatically reduced cross-infection with highly transmissible and virulent strains such as *B. cenocepacia* ET12. Most new cases are

sporadic and are caused by unrelated strains. Since healthy humans and animals do not carry Bcc in their gut or respiratory tract, this suggests that most individuals with CF acquire these bacteria from the environment.

Where in the environment? The Bcc share a range of soil and water habitats with *Pseudomonas aeruginosa*, the most common CF pathogen (harmful organism). In particular, Bcc inhabit the plant rhizosphere, which is the area of soil surrounding plant roots. With the aid of their resistance and low nutrient requirements, the Bcc can also survive in polluted rivers, and contaminate disinfectants and medicinal products.

This information carries important lessons for CF individuals and their families.

1. Onions are a victim of *Burkholderia* and not a source. 'Healthy' onions are not affected by *Burkholderia* and are not a reservoir of these bacteria.
2. Similar to their close relative, garlic, onion bulbs contain a potent antibacterial chemical called allicin. This is produced when the onion tissue is damaged (or eaten raw!) and helps to protect the onion against *Burkholderia* infection. Allicin is also what makes us cry when peeling onions!
3. Onions are only a risk factor for CF individuals when the bulbs are damaged (e.g. in harvesting) and become infected with soft rot following exposure to high numbers of *Burkholderia* in the soil.
4. *CF Today* readers will have to take the author's word that the smell and appearance of a *Burkholderia*-infected onion would act as powerful deterrent to handling or any other form of close encounter.
5. The risk of individuals with CF or their families contracting *Burkholderia* from onions is extremely low.

Gene Therapy Update

November 2009

Pilot study for gene therapy

So far, the Gene Therapy Consortium has given 10ml doses of the gene therapy product to three patients and 20ml doses to 13 patients. You will recall that the pilot study single dose will be given to around 30 people with Cystic Fibrosis. The main aim of this study is to assess the safety of the Wave 1 product.

The doses are given in a filtered cubicle through a nebuliser and each patient also has a small dose in the nose from a nasal spray every five minutes. The 20ml doses have taken around 1 ½ hours to administer.

Each patient has any symptoms recorded and has physical examinations, oxygen saturation levels, spirometry, CT scans and numerous blood and sputum tests. The first six patients were kept in hospital for overnight monitoring.

Although the pilot study is not designed or intended to check for efficacy, the clinicians have also been taking a some measurements to see if the single dose is having any effect (at a molecular level, not for clinical benefit).

Results so far

All the patients have had a mild flu-like reaction to the dose with temporarily raised temperature and a temporary drop in FEV₁ (which were noticed more by clinical measurements than the patients themselves) along with other mild symptoms. The response in the

patients who had 10ml was less than in those who had 20ml. The symptoms were short lived and mostly gone in one or two days. One patient felt tired for several days following the dose, another reported feeling better than before dosing, and another went swimming the following morning.

One of the areas of work the Consortium has undertaken was to refine the plasmid DNA (the correct version of the gene) to remove elements which are believed to cause this flu-like reaction, which was also seen in a previous lung trial. The changes made in the plasmid were successful in reducing these flu-like reactions in animal models. However in the CF patients, there is likely to be another important component, namely the amount of gloopy, fatty substance (the gene transfer agent) being delivered to the lungs. The pilot study is using a new and highly efficient nebuliser, which deposits about 75% more of the gene into the airways than occurred in the first trial. Both the Consortium and the CF Trust's Scientific Advisory Committee think it likely that we are now being over-efficient and the lungs are simply responding to the large volume of this material. Once the amount delivered is reduced, the expectation is that the symptoms will reduce (as has already been seen with the 10ml dose) or disappear.

With regards to looking for molecular efficiency (ie. was the CFTR protein made), the intention had been to assess this either two days or 14 days after gene delivery. After the first few patients had this reaction, the Consortium changed the design of the trial to perform bronchoscopies on day six or day 14 because it was felt unwise to give a general anaesthetic (necessary to undertake the bronchoscopy) to people just at the time of this flu-like reaction. This led to a delay whilst this was approved by the Medicines and Healthcare Products Regulation Agency (MHRA) and the Gene Therapy Advisory Committee (GTAC) – two Government bodies who regulate clinical trials and who have very exacting and time-consuming regulations to help ensure patient safety. All new treatments have to be approved by the MHRA and any gene therapy additionally has to satisfy GTAC.

Encouragingly, many of the patients are showing evidence for new normal CFTR protein being produced in their nose and lungs following the gene therapy. In some cases, the amount of protein has been up to the level of that in people without CF – the largest changes ever recorded using any type of therapy worldwide in Cystic Fibrosis. We must be quite clear that this only happened in a few of the subjects.



A scientist at work on gene therapy in the London lab.

Where next?

Although the flu-like reaction is not severe, and not a problem for a one-off dose, the Consortium concluded that it may not be advisable to repeat this dose of treatment monthly to people who have Cystic Fibrosis. The next few patients in the Pilot Study will therefore have the dosing time, or the dose itself altered, to find an acceptable way of delivering the gene repeatedly. This change in the design of the Pilot study means that the likely end date for this study will now be in late spring/early summer 2010.

Importantly, the overall gene therapy programme will not be delayed as a result of this, because based on the evidence and the likelihood that the flu-like reaction can be markedly reduced or prevented altogether, the Scientific Advisory Committee advised the Trustees of the CF Trust that we should proceed with the multi-dose trial. In order to prevent delay, we will now proceed with the preclinical toxicology programme that must precede the multi-dose trial in people with Cystic Fibrosis. Previously, the product for this was not going to be ordered until after the pilot study was completed.



A Research Technician in the Edinburgh gene therapy lab.

This is encouraging news, although as is hardly surprising with a therapy that is breaking new scientific ground, there will always be challenges to overcome. In the meantime, we remain very interested in our wave 2 product, which looks even more promising for the future.

By John Devlin, Communications Manager, Cystic Fibrosis Trust

Medical Conference

Last year's CF Trust Medical Conference for those involved in the clinical care of people with Cystic Fibrosis was held at the International Convention Centre in Birmingham and was once again very well attended by CF team members from across the UK. Over 200 delegates attended the day long event. There were two plenary sessions on improving adherence in adolescents and adults and what has been learned from the UK CF Registry. Workshops sessions covered lessons learned from newborn screening, managing CF in pregnancy, home vs hospital intravenous antibiotics, and a practical session on the UK CF Registry. How far to go with infection control in the clinical setting, and dealing with psychosocial issues when a CF team doesn't have a social worker or psychologist were also hot topics on the agenda.



Professor Alexandra Quittner of the University of Miami presenting the opening plenary on improving adherence

Date for your diary

The 2010 Medical Conference will be held on Thursday 9 September, at the BT Convention Centre in Liverpool. This fantastic venue is located close to the Albert Dock looking out on to the river Mersey, and can be easily reached from Liverpool Lime Street station or John Lennon airport. For details as and when they become available, email conference@cftrust.org.uk

Please note this conference is only open to those involved in the clinical care of people with Cystic Fibrosis. There is no charge to attend. Companies wishing to exhibit should also write to the Conference Manager at the above email address.



Delegates at the 2009 Medical Conference



Chicago Marathon

10 October
Minimum sponsorship £750



Kilimanjaro Trek

17-26 September or 15-24 October
Minimum Sponsorship £3,600

For details on these or any of our other events visit www.cftrust.org.uk
call our Events Team: **0845 859 1100** or email: events@cftrust.org.uk



New York City Marathon

7 November
Minimum sponsorship £1,500



Costa Rica Trek

18-28 November
Minimum Sponsorship £2,950