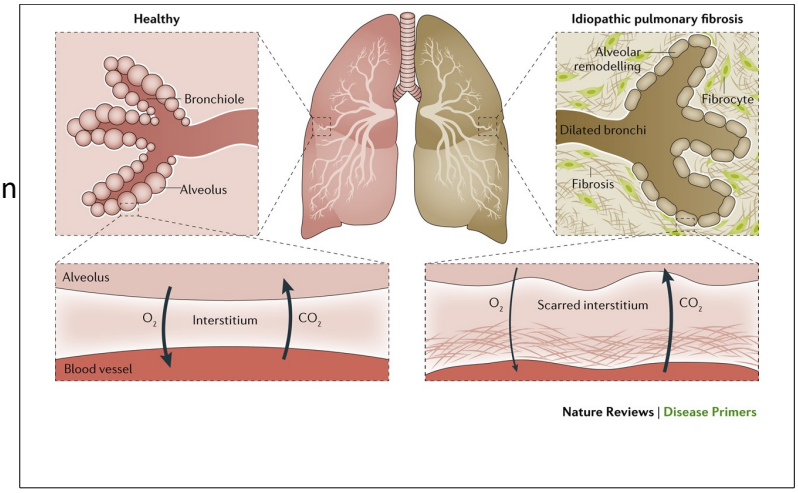
Research Update

A Presentation by Professor Andrew Wilson NNUH & UEA

The function of the lungs is to allow oxygen to be transferred from the air that we breathe into our blood, to be transported to cells all around the body. This happens through a network of tiny airways (the 'tubes' in the lungs) which end in the alveoli, or air sacs. These have very fine walls and are surrounded by tiny blood vessels, into which the oxygen is absorbed, so that it can be carried through the arteries to the tissues and organs, so that they can work properly. The ILDs also include conditions like sarcoidosis, auto-immune conditions (such as rheumatoid arthritis) and some other very rare conditions, which can result in fibrosis in the lungs.

The area around these air sacs and blood vessels is called the 'interstitium' and the ILDs are conditions where this gap is affected. If the gap is filled with cells from inflammation, fluid or abnormal scarring it will affect the normal function of the lungs causing symptoms, typically breathlessness and cough. It is estimated that there are over 200 different ILDs, classified according to whether we know the cause (things like asbestosis, silicosis and farmers lung) or 'idiopathic' which simply means we don't know the cause.



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Undertaking research is a long and expensive process. In order to apply for funding for a study, researchers have to show that there is a question, or problem, that needs to be investigated and answered. They also have to prove that it is actually possible to complete the study – that enough people will agree to take part and that they will be able to continue to the end of the study. This often requires a small initial study, called a feasibility study, before a larger study can be conducted.

The Norwich ILD research programme has focused on 3 different areas:

FaST-MP (the Fatigue in Sarcoidosis, Treatment with Methylphenidate study):

Fatigue, or extreme tiredness, is a common problem for people with long term conditions. When people with sarcoidosis were asked about fatigue, more than 50% described moderate or severe fatigue, enough of a problem to interfere significantly in their ability to cope with daily life. This was far more than in others without sarcoidosis – known as 'controls' in research terms. This feasibility study, undertaken by Dr Chris Atkins, used a questionnaire about tiredness to work out what effect a drug called Methylphenidate (also known as Ritalin) could have. Ritalin is a stimulant, which has been around since the 1950's; a bit like caffeine only stronger. 5mg of Ritalin is about the same as 100mg of caffeine, or about 3 strong cups of coffee. Dr Atkins was interested in working out whether it was possible to conduct a study to test whether giving Ritalin to people with sarcoidosis-related fatigue symptoms, could reduce the level of tiredness they suffered day to day. The study was a Randomised Controlled Trial (RCT), which means it tested Ritalin against a placebo (or dummy drug). The 2 drugs are made to look exactly the same so that neither the researchers or the patients taking them would know whether they were taking the Ritalin, to get a true result of the effect of the drug rather than the effect of taking part in a study, which we know can in itself be beneficial. Almost 400 patients with sarcoidosis were identified and screened to take part. Of those, 23 were recruited to the study, with half receiving Ritalin and half receiving the dummy drug. The study was successful in proving that people could be recruited and no-one had to drop out, so Ritalin was tolerated well. Although, people have previously reported feeling better on Ritalin, there was no measurable difference between the two groups, probably because the numbers in each group were small. It is hoped to do a larger study to find out whether this drug actually could help symptoms of fatigue.

Quality of life in IPF questionnaire study:
There are many different questionnaires which try to measure quality of life in different ways. It is thought that a standardized questionnaire is the best way to find out whether treatments are helpful. You will know that the measurements of your breathing tests (lung function) often does not match how you feel, or how much your breathing problems are affecting your quality of life, and this is recognized by doctors and nurses. This study aimed to try to work out which was the best questionnaire to use in pulmonary fibrosis to measure whether a change after a treatment is meaningful; participants completed several different questionnaires on 5 separate occasions, and the responses were compared. Those of you who took part in this study may remember completing lots of questionnaires, some of them very long! The study recruited 250 with IPF from 7 centres across the UK. Professor Wilson and the Norwich team led the study and Norwich was the biggest recruiter so thanks to all of you who took part! The outcome was that most of the quality of life scores worked quite well but that the shorter, simpler questionnaires were better as they were much easier to use.
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The Efficacy and Mechanism Evaluation of Treating Idiopathic Pulmonary Fibrosis with the addition of Co-trimoxazole
The third big area of research Professor Wilson has been involved in is trying to understand the role of infection in pulmonary fibrosis. For many years, doctors and researchers have thought preventing or treating infection might be important in fibrosis. Chest infections seemed to be quite common and, along with other respiratory conditions, the winter can be difficult with more bugs around and more deaths over the winter months. However, it was difficult to prove that there were bugs present in the lungs of people with PF. Sputum specimens sent for culture often don't grow anything and it wasn't clear if that was because there are no bugs there or just that they don't grow once they are not in the lungs. Now, by putting a camera into the lungs (a bronchoscopy) and taking washings of the cells in the lungs, researchers have identified that the lungs contain the DNA of bacterial as well as human cells. DNA contains the genetic code or 'signature' of an organism; by looking at this genetic information it could be seen that there are a lot of bacteria DNA in the lungs of people with PF. They also found that those with the highest amounts of bacteria died sooner, so it was suspected that preventing infection might be important. About 20 years ago, a pilot RCT study tested an antibiotic called Co-trimoxazole (which kills lots of common bugs) against a placebo in 20 patients with IPF. People were able to cope with the side effects and, at the end of the study, those receiving the antibiotic seemed to have done better, so it was agreed that a bigger trial was needed to investigate further.

A further study began in 2015 to try to answer that question, this time recruiting over 330 people from 43 NHS Trusts throughout the UK (about 1 in 5 of all hospitals), again with Norwich leading the study and with the highest number recruited – many of you will have taken part, so thanks and well done to you all. As with the 2013 study, information about breathing tests, quality of life, hospital admissions and deaths were recorded and participants randomised to treatment (with the antibiotic Co-trimoxazole) or control (placebo) groups. Recruitment finished in May 2018, with a further 18 months to complete the follow up and analyse all the data. The results are only just out and, disappointingly, this time there was no difference between the group given the antibiotic and the group given the dummy drug. One of the challenges of undertaking research in the clinical setting is that it takes such a long time to design a study, get agreement for it to be funded, recruit, follow up and analyse all the data. The "Co-trimoxazole Story" began almost 20 years ago and since then, we have seen big changes in the treatments recommended for IPF. We used to give drugs to suppress the immune system (including steroid tablets) but we now know they are not helpful in IPF (they may help some other interstitial lung diseases) and that they can increase the risk of infection. We have two anti-fibrotic treatments now, Pirfenidone and Nintedanib, which weren't available in the UK before 2013. However, even a negative study, when the treatment doesn't have the hoped for, adds to our knowledge and is of value. We still don't understand exactly what the role of infection is in IPF, but it seems unlikely that taking long term antibiotics alters the course of the disease. If you get signs of chest infection, with increased breathlessness, cough and sputum, then treatment with a short course of antibiotics is, of course, still recommended.

So…time to look to the next study that Professor Wilson and his team will be doing. This time, they are joining

with researchers from across the UK and further afield, to investigate a question we have talked about before – does giving daily antacid tablets (drugs like Lansoprazole) to people with IPF slow disease progression?

Further information is available, via the National Institute for Health Research (NIHR), website on all UK clinical trials. www.nihr.ac.uk

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