Edited transcript of Professor Peter Goadsby's presentation to the OUCH (UK) Conference held on Sunday 24th June 2007 at UCL Institute of Child Health, 30 Guilford Street, London WC1N 1EH

After several years, a few years speaking here, I am pleased that you still clap at the start. A bit of a danger speaking at meetings like this with a large collection of patients, the clapping will get rather thin as time goes on, I'm pleased that people are still here. I think that some of you will have been here before and maybe some of you haven't been here before, so some of the things will be bits of what you have heard and some things that you couldn't have heard because they are entirely new. I'd like to thank the Trustees for inviting me. They do a lot of work on your behalf and it makes it a lot easier for us to do the things that we do. It's always been a pleasure to be associated with this group, we want to get some good things done in this area and I think that we have, but there is much, much more to be done as you know.

I want to make perfectly clear some things, just at the outset, that's why I have made this slide. For the avoidance of doubt as my legal friends say. We have just about completed moving our basic research to California to UCSF. It has become next to impossible to do sensible experimental research here and easier to do it in the US, so that has been done and the clinical work continues here. That is the current plan, there is no appendix – just so everyone understands what we are doing.

Cluster Headaches have come a long way in the last 450 years. Of course if you haven't seen an attack, you haven't been there and many of my medical colleagues find it quite enlightening; sometimes some of the registrars are quite disbelieving, until they see the event. I think it is really terrible, it's like – you know you can't see air and you can't see gravity, but ?? can't understand that people can suffer just 'cos you can't see it. That's the world that we live in, a rather bleak way of putting the fingers in the hand so to speak and so the attack has been sometimes instructive.

These are the various names the condition goes under over the years, and sometimes you will hear neurologists use some of them. They very often use migrainous neuralgia in the UK, because that was the term that was coined by Wilfred Harris, who was a popular neurologist at St Mary's just before the war and during the Second World War. So because it is the UK term, I think they stick to it.

The other terms that have come and gone in their degree of complexity:

Sir Charles Symonds, one of the more famous of the UK neurologists, with that sort of gift for understatement described it as a "particular variety of headache" – that's just splendid! He was an interesting chap. Those of you who come to see us, quite a lot of our clinical work is done in something called Charles Symonds House, named after this fella. So there is some irony in all of that.

Things have moved on quite a lot and I know many of you, as probably most of you don't like the term cluster headache, either because the term headache is so pejorative, it has a kind of "I'm not terribly unwell" association with it. I think we are stuck with this for the moment. Probably it will evolve – I think the primary headaches will all evolve in this way and we'll have better terms for them, but it is not going to happen – I used to think lots of things would happen in my lifetime and now I realise that as life goes on, actually very few are going to happen in my lifetime, I'm just going to perhaps set "fail" on things. I want to talk about some clinical things; I want to talk about some research; and some treatments and then talk about a little few things about the future.
This is some work that Anesh Bahra did some years ago now, but it served very much to highlight this and the next slide, some really important issues that most of you will come across and unfortunately have come across in your travels before you got here and I suppose the most obvious thing to say is it could be worse. You could be living in the fifties, but if you are living in the fifties that means you'd be fifty years older now, so that would be definitely bad and in the fifties patients could take over 20 years to get diagnosed. Whoa that's a long time! Things have come down and it is less than five years now, that's not great, but better than what it was and I suppose that that is something to be happy about.

A number of GP's that you end up seeing, it's probably gone down a little bit, because there is a little bit better awareness than there was. It would be better if all GP's recognised it at the outset. I don't think it's ever going to be like that, because GP's have to do a lot. It would be unfortunate if in 10 or 15 years there wasn't in most large practices a GP who was interested in headache and who would be able to pick it up. I think unfortunately doctors think when they deal with headache patients that this is the doctor, but one of the real unfortunate things with medicine, is that they don't quite understand that's the patient actually and the patient's hair is getting ripped out while they try to get a diagnosis! If medicine understood that the people coming in had the problem, as opposed to the person sitting the seat, the world would probably be a better place.

As I often say to my dental colleagues, the greatest favour you can do to a person with cluster headache is to leave them alone. Even if you just charge them for doing nothing, you would be doing them a favour. As opposed to taking teeth out or doing other things that you do, but I guess if you go see your dentist, that's what is going to happen. I do a teaching course now at the Dental Institute once a year, where I point out to the dentists the existence of cluster headache and some of the other primary headaches and I strongly advise them to do nothing and they seem to be waking up to that broad concept.

My ENT colleagues do what they do which is wash stuff out, nasal stuff. If you go to an optician I guess you get glasses, what can you say, that's what you go to opticians for. Of course if you go to an optician with cluster headache and get glasses, you'll be able to see the world better, but it won't LOOK any better that's for sure.

I'm proud of my ophthalmological colleagues, who in general terms, do nothing, which you should be thankful for them for doing. They just send cluster headache patients away, which is constructive in large measure.

I want to talk a little bit about research that has been going on over the years and more immediate research and I am going to address three broad issues.

I think that the most useful thing that was done on the sort of experimental side if you want, of human research, is this imaging that I am showing you here. The patients did a great job with this, you can't do human imaging without humans and you can't do human imaging of cluster headache without cluster headache patients and you can't image a cluster headache attack without giving someone an attack. Now all of you in the audience will appreciate, better than I do, what that is. That is a big ask and I have always been impressed by your willingness to have attacks, only for the good of understanding the problem generally. We thought at the time this would do that in some measure and it has gone on to do more than that I think. This the first of data that was published in the Lancet nearly ten years ago now, it just seems like yesterday, but like most things time travels fast. And what it showed is a little area in the brain, just here, which seems to be crucially involved. What we are doing here is what is called functional brain imaging, so you give someone a tracer that is labelled with something you can pick up in a so called PET camera, the tracer gives off what's called a positron, the camera picks it up and you can recreate where it came from, because the positron will give off a signal going both ways and obviously arrives at one detector before another if it's this way and if it's about in the middle it gets to both at the same time. So you can recreate where they come from and the images are about blood flow, so they are about what the brain is doing, so when you are watching telly, the vision part of your brain lights up, and when I am dealing with the hospital people, if there was an anxiety part of the brain it would really light up and if there was a frustration one, it would be just red hot when I am dealing with NHS.

But in any case, for example, this part of the brain here is called the anterior singular cortex, it lights up to aversive stimuli it gives an emotional context to pain stimuli. What was important here, was lighting up in this little area of the brain. The little black bit next to it is a fluid space called a ventricle and next to that ventricle, the third ventricle, the area lit up. It's great – I just did an American Headache Society meeting a couple of weeks ago and people interested in this area of the brain, there are people who spend their entire lives, just looking at anatomy and physiology of that

area of the brain. They're interested in engaging in the argument as to what that structure is, because that is an open thing, but that's great, the fact that people want to talk about it in the context and all the lectures are in the context of how that influences cluster headache, that's great, that's going to take things forward. I think that was important. The other thing that was important about this sort of work is that it establishes pretty clearly that your problem is a brain problem, it's not a vessel problem, it's not an inflammatory problem, it's not because you are crazy, or you hate people, or you want to run about with a bad headache, it is because your brain is driving part of the problem. One other interesting thing that was done at the time, which was certainly less painful, is what is called voxel based morphometry. So you take 25/27 people without the condition and 27 with the condition and you basically subtract the brains together. You try to work out what big picture makes a difference in your brain, as opposed to the brains of people who don't have cluster headache and it turns out that this area of the brain has a little bit more grey matter – the brain is made up of white matter, which is the tracks for cables connecting nerves together and the grey matter, which is effectively where the nerves live and you have a little bit more grey matter. Unfortunately, there is no evidence that actually translates into super-intelligence or anything you can sell – in fact, given this grey matter, you probably would be better off without it! But we don't have any way of chopping it out at the moment and you certainly don't want too many people chopping around in your brain! I think we were more surprised than anyone else, certainly I was more surprised than anyone else I know of, when our Italian colleagues decided this was all so straightforward that they would take a person with intractable chronic cluster headache some years ago, and put an electrode – drill a hole in their head and put the electrode into this area of the brain and so they targeted this area and I have avoided giving it a name. There is a structure called the hypothalamus which rather uncreatively sits under the thalamus and in the back of that structure, there are some other nerve groups some of which the names don't matter and somewhere in the back of that the hypothalamus is where they sit, so they targeted and they put their electrode in that hole and turned off this chap's chronic cluster headache. Absolutely extraordinary. I don't think I would have stuck an electrode and been the first person to do it, but well done to them. They have done 16 people. Now this is a list of what is in the literature now of cases of patients who have had, with chronic cluster headache, this is pretty current, certainly as of the American Academy meeting about two months ago. So the Italians certainly published on 16 and have probably done a few more now, a fellow in Belgium called Jean Schoenen has done five, one person got cardio-vascular problems and did not actually get the operation, one person died after the operation which is a whole other issue and it's part of the problem that the brain tissue is pretty soft it wasn't made to have bits of plastic and metal stuck in it – there is a lot of controversy around that as you might expect. Another Italian group has reported a couple – this was in 2006 – a guy called Phill Starr who is a neuro-surgeon at UCSF has got three cases I am aware of and a fellow called Black from the Mayo clinic has reported two and I know of three cases that have failed.

When you go round talking about the successes, someone will put up their hand in the audience and tell you about the failures, so one collects them.
But all in all it is a huge change. If you had asked a person ten years ago, would you have taken someone with a so-called primary headache like cluster headache and stimulated their brain to try and treat them, everyone would have thought you were crazy, completely crazy and I think that even the imaging people thought we were crazy to even try. So it is extraordinary where we have gone in such a small period of time.

One thing that has emerged – it's quite interesting at an understanding level, it's argued about the importance of this area in the brain. Certainly if you can stimulate it and that probably turns it off, it's probably over-stimulation if you want, what's called de-polarisation blockade. You blast something and it doesn't work as well. It is probably important – it turns out I recall going to one of my neurosurgical colleagues at the time when all this was starting and showing him this picture and saying well – he's a stereo-tactic surgeon who does brain surgery with electrodes in patients with movement disorders like Parkinsons and I asked him whether this was technically possible and he leapt out of his seat and he grabbed a book, as you do, and showed me a chapter of his in a book an he had been doing, in Sweden before he came here, so-called psycho-surgery on patients with really weird behavioural problems. They would go round the place strangling cats or taking bits of glass and sticking them in all sorts of weird, seriously weird and unmentionable places and just very weird

behaviour, self-injurious aggressive – and what they were doing and it was described in the 1970's, is making lesions in what was called the area of Sano, because Sano was the first person to describe this. It turns out it is the same area, they were making lesions bilaterally.

Now what they noticed is that when you start to turn the electrode on in these patients and this was 30 years ago, that the patients become aggressive, restless and agitated and want to move about and the neurosurgeon's noticed that if you are trying to do neurosurgery, having a person moving about and struggling is very unhelpful! You know it is better if they are still, if they are moving its bad enough as it is, but it's worse when they start struggling when you are trying to drill in their head, or put stuff in their head. So they learnt very quickly to anaesthetise these patients. But when I heard that, I said to myself isn't that fantastic. Here's an area of the brain that you come to by imaging the attack and you come to it from another place where people are putting electrodes in, what's the behaviour, this terribly stereotypical behaviour of anyone that you have seen in an attack – very agitated and very unpleasant and it brings it on to a whole new plane, because it starts to ask the question whether the brain area drives the behaviour to some important extent and understanding the way brain governs these diseases is really important ultimately for understanding the disease. So I think that maybe this imaging has done a number of things to help that go along. That will translate one day into a better understanding of your disease. At the moment it is at the level of understanding. And as I say, the therapeutic side is clearly with these stimulations.

I'll return to stimulation when I am talking about the future a little bit. I want to talk about what has been achieved with treatment trials, because the number of options with the treatment with acute cluster headache are limited, as you well know, and even the ones that are available, you have trouble accessing them and life is bad enough as it is.

This is the first of a series of treatment trials that we were involved with – you were involved with – a study on intranasal sumatriptan. Injectible sumatriptan, as most of you know, was studied in cluster headache during the development of the so-called triptan and clearly effective and it works very quickly for most patients. It is a really excellent step forward and you could say in many ways – if you look at the responses of cluster headache and migraineurs to triptans, clearly it works better in cluster headache patients, broadly speaking, if you look at the population, or you look at the rate of onset when it starts working in migraine – we can talk about why that might be.

This is a double-blind – if you want people to believe stuff, you have to get out of your own belief structures, so the way these studies are done are called double-blind. That means that the patients and doctors involved don't know what is being administered. They are placebo-controlled because one of the things you take is the drug and the other one is something that matches it to give the appearance of the drug, that's called the placebo. This is a cross-over study, meaning that one person does both things, treat the placebo and the active treatment. The other type of study is parallel groups. Government and European Medicines Agency and the FDA in the US, prefer parallel groups, little bit because that's the way they just think and that is why. I think that there is a lot to be said for a crossover study – it understands a lot about I think about responses to the drug, if you test both the drug and the placebo in an individual.
At any rate, for most migraine studies you use a two hour end point. For cluster headache more than 30 minutes – that seems like rather a long time, as you better appreciate than I would. A response in these studies means that you get things improved, but they don't necessarily become painfree and painfree means what it says on the jar! The sumatriptan 20mg ?? published in a journal called Neurology a few years ago. This was never licensed as a licensed indication, because there's not a lot of interest in industry really in your problem, because it is considered to be rather small, although the UK prevalence of cluster headache is about the same as the UK prevalence of multiple sclerosis, we think. We'd know precisely but for something I shall return to in a little while as well, but is about 0.1% - that's what we think. We can't be really sure about that. It's an important issue obviously, because the size of the problem drives the industry's interest. We got a clear response, publish that in the journals and recommend its use. We became interested in zolmitriptan because it's absorption rates are better. This is zolmitriptan in the nasal cavity – this is what PET – again one of these positron things with the zolmitriptan label going into those, so we went on and did a study here that many of you would have participated in with our European colleagues, and it was published in the

archives of Neurology last year and we did this as a three-way crossover, so placebo, 5mgs and 10mgs of zolmitriptan. In the world of science and pharmacology and medicine, what's called a dose response – so a greater response for taking more medicine is considered to be a marker of legitimacy, if you want, of a substance use in a particular clinical indication, so you can see there is dose dependency here, and you can see the placebo response at about 20%.

Placebo doesn't mean crazy – placebo is a very complex combination of things. I think it is partly, in headache, about the attack finishing at any rate, because not all the attacks go to exactly the same length; I think it is also clearly true that all attacks stop – big picture. So you might expect their brain mechanisms to stop them. At any rate, we got really quite handsome painfree responses – again at 30 minutes and I gave the protocol to my American friends, because to get a license for a medicine in Europe and again the US, it is said – the government regulators like two separate studies, because they think one just might be chance, and so this, as you see, is more or less the same result. This was presented at the American Academy of Neurology and came out in a journal called "Neurology" and they took the same design and got effectively the same result, which is now two, what are described as well-powered placebo controlled trials. Perhaps it will get a licence. Certainly the evidence is over-whelming. Why would that be useful? Because a way of stopping you obtaining treatment, is for people to turn around and say there is no evidence for "x". Very often its about money gate-keeping rather than intellectual pursuit, but if that is the challenge, then one of the ways of meeting the challenge is placebo-controlled trials, because then there is evidence for "X" and the argument then can only be that I am too cheap to prescribe it! Which is not really about the doctor so much as the way the NHS works, I suspect.
You've heard a lot about oxygen this morning. It's an interesting thing that you see on here the sum total of the well-controlled clinical trials in oxygen to date, the princely number of 19 patients in a study published in the archives of Neurology more than 20 years ago – that's it! That is the literature! This is why there is a lot of grief and aggravation around, but its one of the many reasons why there is grief and aggravation around oxygen. People could very reasonably say, well the evidence is a bit thin and it's a bit old.

This was a crossover study, this was the priority end point – a pretty reasonable end-point. Not everyone completed the crossover, though that wasn't entirely clear, but it clearly did better than taking air. And the response of 15 minutes too, that was quite reasonable. But there is quite a criticism on a number of grounds; the diagnostic side because the study was done before the IHS promulgated its criteria and it is very small at only 19 patients. It is one of the reasons we undertook a proper placebo-controlled crossover study in acute cluster headache to try and make it absolutely clear that there is evidence and the only thing that is stopping it's use is logistic. And again to drive interest in the medical community around the subject.

So this is the study Anna Cohen has led on and Brian Byrne has been involved with, for which we are grateful that eventually 76 patients completed a 150 attacks – this well-powered, everyone will fall over themselves, randomized double-blind placebo-controlled, so totally righteous. Two periods, so we could get more power so to speak. In a relatively rare condition, instead of having a person treating one or two attacks, if you get them to treat four, you get more data from the study. So we got a lot of data – I am showing you the placebo response rate, which is about in line with the zolmitriptan studies unsurprisingly. I can tell you that the study is overwhelmingly positive and Dr Cohen will present it to the world – well the headache people think at the International Headache Congress with all 1,000 headache – you know the afficianado's of the world, in fact we understand it is just a small microcosm of crazy people who are really interested in headache (laughs) in Stockholm next week. So it will then be in a very public mode and we hope that by producing a really well-powered study that is overwhelmingly positive that people will stand up and say right – OK that's a done deal, now the question is how do we make sure that more people with the problem get access to proper treatment.
How do we work out what the best flow rate – there are all sorts of questions that come next, but first you need to get to first base. And we are at first base.
One of the biggest frustrations with the study, I have to say, was perhaps was paradoxically one of the good things about talking about oxygen over a number of years – you can't do a study of people who have already had oxygen, because if it doesn't work, they are reluctant to go in the study –

that's obvious – and if it does work they go in the study, but then that enriches the study for people for whom it's going to work. So you can only really do the study in oxygen-naïve people as far and as reasonably you can do that. That is a real problem, because through the excellent work of OUCH, oxygen is getting more widely promoted. It's been difficult to do, I think it would be impossible, nearly, to repeat. Fortunately the rest of the work after this won't have that limitation. So we think that will create a bit of – I hope it creates a little bit of interest in Stockholm and certainly we can leverage it up into the general medical community to make them more interested in what's a really important thing and there is data!

Long term treatment:

For some of you chronic cluster headache sufferers, I mean, that's just awful, it is such a dreadful condition and to have it chronically is really awful and for the longer episodics, so to speak, then I have greyed out most of the things, 'cos I don't really want to specifically talk about all of them. I just want to point out something about verapamil that many of you would know, but I think it is an important public health thing in the context of verapamil.

You use very high doses, I tell my neurologic colleagues we use neurologic doses of verapamil, we don't use cardiac ones, so don't think you can leave it to your cardiology friends, you have to think about it.

It works pretty well, as many of you would know, constipation can be a little bit of a problem. A number of cluster headache patients have looked at me over the years like I was a complete idiot, as I told them about constipation as though "yeh, well so what? In comparison to the attacks?" But the way one practices medicine is to tell everyone what is going on.

Leg-swelling; those of you who may be here, or others who have had the problem with the gums or even lost teeth and I have certainly seen patients who have lost teeth with it, will appreciate that problem.

We are pretty diligent about the ECG business. For this reason, it's a paper that is in press again in this journal "Neurology" which is a general neurology journal that is very widely subscribed to in the world. It is about cardiographs. The problem is that about 20% of patients with verapamil, will develop changes in this part of their cardiac trace, in your heart tracings, so it is a tracing of the electrical activity of the heart and what happens is that part of the heart where the pacemaker is – represented a little bit by this wave here, the so-called P-wave turns things on and then the large bit of the heart, the ventricle, follows that, so there is what is called atrio-ventricular progression of the signal. Now, if that gets delayed, then that can cause the heart to misfunction in many ways and you will see perhaps here, this is a normal sort of length and then the length from here to here is obviously long – called (because that's the P-wave and this the QRS complex) it is called the PR interval and when it gets too long, its bad for the heart. It is bad in that it can cause the heart rhythm to become irregular and that's unhelpful and you can see that this is something that happens on verapamil to about 20% of patients with clusters. So we have to be pretty careful – this is on 240mg a day. It gets better or it goes away if you stop taking it. It is a really tractable thing, it would be really interesting to try and sort out why this is, but it's been tracted and its not been sorted out at all, but it can be monitored.
One of the things I will emphasise on this slide is that even people with stable dosing seem to be able to develop these changes, when left alone. This is a person who we didn't see from one year to the next. So it is our view, supported by – well it's very reasonable data I think, that verapamil shouldn't be used without ECG monitoring and certainly people shouldn't be left indefinitely on it without ECG monitoring. Its pretty cheap, it's pretty straightforward to do and it saves a proportion of you quite a lot of problems. It is quite a thing we have tried to push with our neurologic and medical colleagues and something you should be aware of if you are using the medicine.
So, the future – what of the future?

The Orange man says "the future is bright" – well there are some good things and some, shall we say, challenging things.

MRC is the Medical Research Council. Medical I emphasise, because that would seem to be things to do with medical problems, not always obvious, but there we are.

We proposed to them, some little while ago, we had some discussions with your Trustees, to work out what the actual prevalence of cluster headache is. It is easy to succumb to the criticism that it is not as common as you claim, or it's not as important as you claim, if you don't actually know what to claim. And people will say of course, that the patients you see in a place like Queen Square, well they are selected and they are special, blah, blah, blah. Yeh, they are special and they are selected, you know there is suffering of the unselected ones. The estimates currently vary from 0.09% to 0.3%. Now most people think that 0.3% is a wild over-estimate. When you think about it – 3 per thousand – that's a lot of people, a lot of people and you are quite a very successful group, but you are nowhere near, you are not even near one per thousand, unless you have had a big rush of membership in the last couple of weeks. There is a big disconnect there. Does that mean that the estimates are bonkers? Or does it mean that there are tens of thousands of people with this problem that don't even get recognised? Is that what it means?? There must be a responsibility on those in the tent to make sure that if most people are outside the tent, are not suffering more than they need to suffer.

So we wanted to do a population based study, random sampling – we wanted to do it within the M25 because it was thought it would make it – one of the problems if you start doing a population based study that includes Northern Scotland, it is actually quite challenging to verify the diagnoses, to see everyone, do things properly, so for reasons of unfortunately its not meant to be London-centric, but its just a question of geographical convenience.

We wanted a questionnaire study and then we planned a clinical interview and we thought that by doing this we would have a population-based cohort to study, because of the criticisms that comes up if you do a study is people say, well, you did a study of zolmitriptan, you did in patients who came to your clinic, so they are not really real patients, they just come to your clinic, they've got blood and stuff – they seem real to me! So the criticism is you should do everything from a population basis. It is like anything in life, if you want to find a criticism, you'll get a criticism.

We put that into the MRC, they said it we didn't make it clear enough what the response rates would be like and for the third time we went around the houses. My impression is – and there are good response rate data for migraineurs – my impression is that cluster headache patients are no less likely to respond than migraineurs, no less better-motivated, no more stupid and no less capable of filling in a questionnaire, last time I was there. But the MRC people thought perhaps that you were not well-motivated, not interested in your condition, perhaps you didn't want to fill in a questionnaire. They obviously had never, ever, met anyone with the problem.

So we put it back in, addressed those criticisms and I got the feedback from them this week, which I am afraid to say is not very good at all. This is what they wrote, they said:

"The proposal is not sufficiently….." Well you can read the rest, and the panel's decision is final and not open to appeal.

I just want to read you something that the most critical reviewer wrote, so you understand the sort of people that you have to deal with, this is the most critical reviewer – you score MRC grants on a scale 1 to 10, where 10 is stellar, exceptional; 1 is serious concerns. 6 is good quality, nationally competitive, addresses a reasonably important question, will be productive, if it had a problem could be corrected easily. This guy has scored 6, this is the worst score, all the other scores were better: "The rationale of the study is correct. It's fundamental to start from prevalence data to plan public health strategies and therapies. I agree with the proposed method consisting of population-based study of households with a questionnaire approach. As the problem in hand is about rare pathology and differential diagnosis, the level of the training of the individuals is fundamental, presence of these conditions it varies from 0.08% to 0.2% in a population-based study of 30,000, you might get 60 patients and in my opinion the design and methods are positive blah, blah, blah…."

It concludes:

"I know it would be difficult, can I suggest that you study more households."

So the most critical person had to say that actually they should give us more money. I had to say, after I read this, I just don't understand. I do understand a little way. The problem is a problem that you and the Trustees are going to have to face. If people don't think that this problem is important, they will not do anything about it. They won't do anything about it. They don't have any criticisms, they just go on that its not that important. I think it is that important. But I can't convince governments of that and I can't convince the MRC of that. You have to do that, because it is your problem. You have got to get a hold of these people for whom you pay taxes and who amuse themselves on your behalf and you've got to shake their tree, because they don't think your problem is important. You have to convince these people that your problem is important, or we are not going to go anywhere. So, good and bad.

Let me talk about CGRP's. Why do we talk about that?

A significant problem with the triptans, is that is that they constrict, they clamp down blood vessels, it is unlikely to be part of the mechanism of action of triptans and cluster headache, I think that's just presposterous. What they do among other things, is they block the release of the peptide – calcitonin gene related peptide – the triptans do and it seems important in the transmission -if you want - of pain signals within the head. Seven years ago, we showed that calcitonin gene related peptide was elevated here, as you can see in patient's with migraine – not some other substances I won't say too much about.

That led – I must say it took a long time – but that eventually it led to a study – the development of a calcitonin gene related peptide antagonist, rather uncreatively called 4096BF and it certainly didn't turn out to be anything like its namesake. To our response rates, this is a parallel group intravenous study - placebo in the blue. So CGRP receptor antagonists work in migraine. Why would you be interested in that? Because we, and the Italian groups studying the same groups have shown that CGRP is also released during acute cluster headache. Someone's causing trouble – so it's released and just about two weeks ago, the Merrck people produced a study, a migraine study – this is a randomized parallel group study, placebo controlled, escalating doses, compared to a triptan of the Merrck CGRP antagonist and it works in migraine. Why am I saying that? It means that there are a couple of companies at least, who have got CGRP receptor antagonists, these things do not affect blood vessels, they don't constrict anything, they won't hurt your heart, they won't give you a stroke and you know, sad as I have to say it, they won't be a big problem for smokers and as much as I would like to encourage people to stop smoking, for many of you that would be quite something to know. These things will come along and they will get studied in cluster headache for sure, because most of us involved in advising these companies, is just to pester them all the time about it. So there will be new treatments and they will be really helpful, particularly for those of you who have cardiac heart problems, or had strokes, where we can't prescribe triptans any more and you know if oxygen doesn't work, you are up the creek without a paddle. But we are going to have a new paddle and its going to come down the creek in probably about three to four years – its bright and its important.

What is happening on the surgical front?

Well over the years the surgeons have been right into cut, slash and burn. If you got pain on your face, just cut the nerve. That's got its problems. The burning, is thermo-coagulation of the trigeminal ganglion, so you stick an electrode on the ganglion and burn. All the cutting, slashing and burning approaches, the necessary thing is it reduces function of the nerve. So for some patients, it will result, for example in corneal irritation, because you can't blink – the blink reflex gets inhibited. Unfortunately, with this root section, this is the Mayo Clinic root section experience – some people get this thing called anaesthesia dolorosa where you can't feel that part of your head as such, its like anaesthetic, but its got a burning dull intractable pain – very helpful! And like most things dealing with the brain, from time to time, if you get it wrong people die. Of course that is very effective at

stopping the attacks, (laughter) but it's not an outcome I think we want to sell. Certainly it would be a good health economical outcome, but it goes to show you how crazy those people are!

We became interested in the occipital nerve. That is obviously – this is not a person as such. I mean most people don't turn up with their occipital nerve so easy to find like that (laughter!). It's not that gory, it's a little gory I suppose – it shows you what we do. Michael Anthony who is an Australian neurologist taught me to do this. He is so believing of greater occipital nerve injection, he used to get his senior registrar, which I was on one occasion one year, to inject his occipital nerve once a year and he said he never got a headache. I think it was quite a crazy thing to do, but injecting your bosses head was a whole other deal. He kept his hair quite short, so it was easy to do. Those of you who have had this you will know that for some people it is exceedingly useful and for some people it is useless. If it happens to be useful the injection is more or less without side effect. As I tell my registrar's and fellows, if you take the needle and you wooft it in front of some peoples face they will faint, so it's helpful not to do that – and we have had the very odd person, its hasn't happened for years and years, it's a real drag that it happens, a little bit of hair loss just here. I think the injection was too high – I didn't do it I have to say, I hasten to add. The biggest problem with this , I think, is the poking and prodding you are doing before having it and the next biggest problem is probably getting it done in a timely sort of fashion.

The occipital nerve input at the back of the head and the input from the front all go to the same place in the brain. We became interested in how that might be useful in cluster headache and so started stimulating the nerve with a stimulator device, which has been useful, I think, I have to say. This is work that Brian Byrns was lead author on, coming up in the "Lancet" a little while ago, caused a little bit more interest in the subject. These are the first eight patients that we stimulated. Bearing in mind that they are people with medically intractable chronic cluster headache, in the main, who really have a lot of problems, and we've got reasonable follow up and it had all the usual suspects. It is interesting that occipital nerve blocks don't actually predict the outcome to the stimulator, which is a bit of a drag. We were kind of hoping that you could work out who should have it and who shouldn't by doing the blocks, but you can't, so it's nice to have good ideas, but it's better if they work!

This is what we found out, some patients think it is a spectacular thing, some patients think it is moderately spectacular, some go hum-ho and some don't get any effect at all. We have learnt a number of things about this, we certainly learnt that if the battery fails, or there is a problem with the leads the attacks tend to come back, so that is quite - it's not helpful for the patients I have to say, I understand that, but it's helpful in terms of understanding what the thing is doing and also as a kind of proof that it is doing something useful. It can take some weeks or months to have its maximal effect, so we can't do short term stimulation to work out what is going on. We've got 13 people now who have been implanted and the outcome is more or less the same.

The Belgian outcome is the same, Jean Schoenen and Delphine Magis reported this in "Lancet Neurology" recently, so it seems generally true, that a proportion of people with medically intractable cluster headache would be substantially improved by this procedure and that needs to be better, perhaps more extensively studied and also more easily available I suspect, because it is relatively innocuous as a procedure, as many of you would have seen if you saw it demonstrated last year *(year before)*.

So where are we up to. I think, you know, things are pretty good. It's easy for me to say that, because I don't have headache and I appreciate I don't have cluster headache and I appreciate I don't have to ring up the hospital to get an appointment or I don't have to fight with my GP to get a bleeding prescription, I don't have to convince someone I am not a lunatic, or I don't have to convince my employer that I am not shaking a leg – but the condition is better recognised, those that come after us won't get as bad a deal as you do. I think the understanding is just completely awesome. In the last decade it has just gone from vague idea there is some inflammation of somewhere in the base of the brain to understanding it is clearly a neurologic condition, it belongs in the hands of neurologists, they have to pick it up one day. It might feel a little hot to them, but they are going to have to do it, because it is a brain problem, that is a quantum leap, that has even led to

the brain stimulation. I think the treatment business is better. You know, we have got placebo controlled trials – there are many conditions that just have opinion. We've got studies, we've got data and eventually that will drive people to do what they should do. I think the options are going to get better in the future. You have seen one of them and there are many other things that are being worked upon.

I think the big challenge is going to remain convincing governments, the profession yes, but more government people I think, that the problem is sufficiently important to put resource behind. If you never understand how many people are – its like if you ????? you will never ever see the problem and I suspect that's the way that the government would like it to be. There are challenges for you, there are challenges for us that are obvious – we have to make sure that our colleagues understand the problem, and they understand that treatments can be available. As I have said in the past and I will say it again, it is a privilege to work with your group – the sole purpose of the exercise is to make the world a better place for people with primary headache, that is my mission statement and I'd say it is achieving that – its difficult because things are under-resourced, I could babble about that all day and I don't intend to complain about that at length, it is challenging to provide the sort of things we'd like to provide, because we are completely under-resourced to do it. So when people don't answer the phone, or they don't immediately get back to you, it's not because they don't want to, it's because they are simply horribly, horribly over-taxed by what is an important problem, but needs better recognition from the people who actually owe their business to you – that is the government and such representatives.

Again it is a pleasure to be here, I am sure things will move ahead in the next year and I am sure it will move ahead by a good partnership between ourselves and you the patient group.

Thank you very much

Questions from the floor

MRC Funding

Yeh the way you put up grants, is you have to do a budget, so you have to cost out what it will cost to mail, what it will cost to process the questionnaires you get back to see the patients, etc, so yeh you are asking for a specific amount of money, I don't recall what the amount of money was off the top of my head, it wouldn't be more than £800,000 or something like that over four years. I mean, OK, that might sound like a lot of money, I actually don't think it sounds like a lot of money to work out whether 0.1% of the population have a problem they don't know about, but if you keep your eyes shut you will never know. So you do have to set out a quite clear budget for doing that. They always say that, that standard letter, but like most things in government, the rules say you can't do something, unless someone in government says you can. So politicians change the rules all the time. We just need to get them to change it! Just a bit cynical but there it is. 'Cos if they said everyone can appeal, you can imagine what would happen, everyone would!

!When using the nasal sprays cause damage the lining of your nose?"

Yeh, that's a good question – good practical question. No, as far as we can tell. When the sumatriptan original nasal studies were done, not everyone had, many sites had patients go along and have nasal examinations by ENT surgeons and the examinations afterwards and they had no consequence to that. There are only really couple of – at most three – uses, so that is a bit limited. The zolmitriptan people did the same thing in their migraine studies and they did it in follow-up, so they didn't see any changes in the nasal mucosa either. I am unaware of any report in the literature of any long term effect, and usually bad news spreads fast, so if you get a hole in someone's nose you take a picture and send it to the BMJ and people love to publish bad news – bad news drives the world. So I think by and large in the round, the evidence that has been collected is that it is perfectly

safe and that negative fact that nothing significant has ever been previously reported would suggest to you that, yeh, that's not an issue.

But these sprays now have been around for the better part of, well the sumatriptan nasal spray for at least fifteen years, so I think if there was going to be a problem it would come out, it would have already emerged – I think within the limits of using them two or three times a day. You are in a good position in cluster headache, I guess you are almost in no good a position!, but if you have the episodic version at least you have the benefit of having long breaks, so that acts in your favour, the migraineurs don't get that in another way.

"On the back of the Imigran it say "not suitable for use by patients over 65" – the injections – is that true?"

We all are, but as I get older I realise that those rules are both arbitrary and, I hope, irrelevant. The basis of that is that no-one over the age of 65 knowingly was put into any of the clinical trials with triptans. That was a safety thing and it was also industry protecting its back, because they didn't.... Triptans were developed for migraine. Migraine is a condition of young women – 30–40 year old women (I shall emphasise that means young!) and so they didn't want to get themselves in trouble by having too many 65-70 year olds in the studies. So 65 is the upper limit. So all the safety data was collected that way.

Now when you go for registration of a medicine, you supply them with the clinical trials you did and you are registered on the basis of what you did in the clinical trials, so if you studied 18–65 year olds in the clinical trials, you will be registered for 18-65 year olds, that's the way that the system works. There is extensive – what's called off-label, because if it is not on the label use of triptans, in the over-65 year olds. Now, and I think it is a well-accepted position, which I would even say, you could even get away with saying it in the US without being sued too much, or too often – that it's a very individual decision once you get over the age of 65. If there is no contra-indication, I think it is just a protection thing that the industry put on the back of the box. I never stop people having triptans just because they are 65. You know there are 50 year olds who are walking around a cardio-vascular disaster area and there are 70 year olds jogging down the street, who make me feel breathless when I watch them! I think that it is a sensible partnership between the patient who you tell what the story is and the doctor, who says fine, well what are we going to do, stop you taking them because of that, or continue them. So it is a relative thing. Doctors can use drugs off-label, provided that they have an adequate explanation to the patient and provided that their colleagues would think that was a reasonable thing to do, so using off-label high dose morphine the way that chap did in that place in Hyde or something – everyone thinks that's pretty dodgy – no-one does that, but using triptans at 67,68 is not really an issue, unless they have a cardio-vascular problem, and then its an issue whether you are 25, so it is relative. I have gone into it in a bit of detail, because it comes up quite a lot. We see people and advise it, not to make an issue of it.

(Cannot hear questioner)

Life is complex. There is a lot of information about it, I can tell you that there is many, many less patients we see who are 90, then patients we see who are 80 and patients we see who are 70 and 60. I can tell you that the natural history of the condition seems to be to go away, more than people just die. I can tell you that the oldest person I have seen is 96 with cluster headache, who had had an 18 year break from his previous bout! And you know, he came to see me, just to tell me that, which I was quite grateful for in some ways, because you know he was saying that well 18 years is a long time, I have to agree, and 96 is good age and I would definitely agree with that and you know if he died when he was 95, people would have said that the disease had gone away, but it really didn't, he just got lucky and lived till he was 96! So may you live till 96, or 97 and if you have a 25 year break, just drop us a note, because then I will be able to tell the anecdote.

The simple answer to the question is that in general terms, the propensity seems to never actually go, but you have got to try to get it going. The other part of the 96 year old story is he had a heart problem, he was admitted to hospital and had nitro-glycerine infusion for the heart and that, as those

of you who have been in studies or read anything will realise, a couple of puffs of nitro for most of you in a bout and the attack will be off in about 10, 15, 20 minutes later. But he had an infusion over several days and that reactivated things. So if you need your heart treated, that's fine, but since you are a lady, the chances that is going to happen are much less. And in general terms, we will just be optimistic. But the natural history is to ease. Unfortunately it is a condition of the young, productive, tax-paying years, the third thing I say to place emphasis on the need for those that receive the tax to give you some of it back in research budgets.

"I went to see a headache specialist last week and the prescription he gave me included the verapamil which is MR and some people here have said it should be BP and I just wondered what the difference was and what your opinion would be on that?"

MR is the long-acting one. You know there is – this is just an opinion, it is not placebo controlled. Remember placebo control has got a lot of influence and opinion is a whole other deal. We have generally found the long-acting verapamil not to be as useful – *in general terms* – that is a general opinion. Maybe the person you have seen has had good use out of the type that he gave you. There is nothing wrong with asking the question whether you know, what they think about whether spreading the dose out is a better thing. We generally think that is true – its an open question I wouldn't be dogmatic about it.

"Mixing triptans"

Well I think that for an attack, mixing triptans generally speaking isn't helpful, generally speaking. Because by the time you go to in general terms its better to work out which drug works for you and then use the drug that works for you.

In general terms there will always be some individual exception to what I just said, because if there were five rules I could write down, then you wouldn't practice medicine, you'd just be a monkey and you'd just read the rules. So, I mean it is important, if you see an individual they are individual, there will be reasons why you might want to one thing in an individual but not in another, that are very clinical. But that is the two edges of that sword.

In the middle in general terms, mixing triptans is not a really clever idea, but so in general terms we don't do that. I can see how some people might, for example, use a spray at the beginning of an attack and when they weren't getting anywhere, want to go on and use an injection. I think it's probably better in general terms to try not to do that.

"but specifically Frovatriptan?"

Oh – yeah. I wouldn't generally mix frovatriptan and imigran, because Frovatriptan's action - Frovatriptan hangs around the body a lot, I don't' think that that is relevant to its action in the acute sense, but in the old days, what people used to do to treat cluster headache is give daily ergotamine, as a preventive. And Charles Symonds used to write about that. We don't do that any more. It's got difficulties with daily ergoptamine. Frovatriptan is not much more than watered down daily ergotamine at one level. I would think if you do that, if you mix Frovatriptan and an acute triptan, then what you may end up doing is getting some interaction between the two. So in general terms I wouldn't do that. You know it's a bad thing – well not bad, but it can be unhelpful to generalise to everyone on the basis of one person, so I guess I would say to people writing on the bulletin board, it's great to share experiences, but one shouldn't be dogmatic that everyone should share them with you, the sort of plural society we live in. It's why some people like to buy the Daily Mail I guess! Sorry – I had a few funny things from the Daily Mail health guy, whenever you say something to him, whatever you report, it is almost impossible that it will be actually reported accurately – God!

"I came to see you last, a year and a half ago and asked about stopping verapamil. I was then primary chronic, I finally stopped the verapamil in May last year – I haven't had another attack since..."

Good

"So, could they have stopped before that because the verapamil...." (cannot hear rest)

It is actually, about 15% of patients with chronic cluster headache if you look at large databases will transform into the episodic form over time, so that's good. That is a well recognised phenomenon and you know whether the verapamil had any effect in prolonging your chronic cluster headache is an open question for which I am agnostic.
You know I think it is always useful when dealing with medicines to think about withdrawing them from time to time to be sure that the effect you think you are getting is still the effect that you are getting. So, you know, one of the things I'd love to do – it was one of the things I was hoping to do on a population basis, is instead of having to rely upon – and I respect what you are saying as an individual – but instead of relying on individuals, try to get out in a population to people who normally you wouldn't talk to, because invariably the people you don't chase that have other information that informs things for the general group and I think that that's – it'd be nice to get onto the next level, so that when I diagnose someone who is 15, I would really like to have information about ordinary people and what's happened to them over the years, because all these sorts of question you ask are the right questions, and we have information, but it is all rather limited and it's all clinic information and I would really like to have better information to be able to tell you. We just don't at the moment.

"Two years ago there was a talk on research into genetics and has there been any more work done on that?"

Well there have been a few more studies. They have come to she same conclusion. They have come to the position that the what are called polymorphisms, the gene abnormalities they initially identified don't seem to be relevant in cluster headache. The ones the Italians had identified are what are called hypo-cretin receptors or orexin receptors. The genetics of cluster headache hasn't advanced much beyond that, largely because the techniques for looking a conditions where there are not strong families, are not as well-developed as they could be. Again, I don't want to sound like a broken record, but you need to address that on a population level to deal with the statistics of it. One of the things that you could do with a population-based sample is trying to address that.

The other thing that would help, is the eventual – and I hope that will happen one day by habit, by doing talks and going round the place and asking – you will run into the family that says that there are seven people in the family who have got it. If you get a large enough family, that will be the thing probably that breaks the ice. But you have just got to keep on talking about it until the family emerges. Sadly, as you probably realise, because there is so much misdiagnosis. That's quite a challenge, but no we are not actually the genetics is not much more advanced than it was – no it's not advanced at all, more than it was two years ago.

"Has anyone looked at prior head injuries as a possible factor in the development of cluster headache, possibly even decades or so?"

In our cohort, when we first looked at it, we had some information about that and didn't see any particular signal coming out of it. The Italians have got a large cohort and Benzoni (??) doesn't see that coming out as a signal. Having said that there are a sub-group of people who had trauma just involving – around the eye – where there does seem to be some initiating event, but it is almost always just above the eye, so called supra-orbital trauma. There is a little bit in that literature and a little bit in the literature around eye surgery that would suggest that a possibility – not for apropos the last question not for everyone – but unfortunately by the time you have had the trauma , it is too late not to have it and most people would opt not to have head injury at any rate, so it doesn't take us anywhere in particular, but there is a small group. The really reliable stuff seems to be this supra-orbital – above the eye – trauma.

"Cannot hear question – something about off-label prescribing of Calcium channel blockers "

Yes, very off label. In the main cardio-vascular indications are up to about 240mg a day. And I say neurological because I use it to place emphasis for my neurologic colleagues that it is something they need to be interested and involved in, that you can't just sort of forget about it and you know, 'cos it's an old drug and you know its pretty safe and so forth – just to create that responsibility around the use of it. As you say, off-label use is complex, because off-label use – as a physician you can legitimately say well I don't know enough about that so I am not going to do that. I think I can understand that. I think it speaks to the bigger picture problem, which is – why is it that in an organised National Health Service (and I put that in inverted commas) that substantial neuroscience centres in this country don't really have any serious headache representation at all, why is that? How can that happen? Why would you have the commonest problem in neurology not represented? It would be like training electricians, but you don't actually mention light bulbs to them – it's too common. And then when they turn up to fix your light bulbs they blow them all up, that would be a real drag and you wouldn't think much of the electrician.

I think that the problem of off-label use is a generic problem in medicine and the way you get around it is you have relative experts in the place where you are and one of the over-riding aims of the exercise, from our point of view is to populate the place that is the UK with people who have an appropriate level of expertise.

Most GP's will go along with you if you provide them some input, so to speak, and you help them along with it. Some will dig their heels in and won't do it and that's unfortunate – there's not much you can do about it.

"Could you say something about the incidence of cluster headache and latitude, it's always mentioned in the literature that tropical countries don't have as high an incidence – is there any evidence to suggest that is true?"

Substantially it's anecdotal. I would be cheered if the government would provide us with funds to set up a sort of unit in southern Spain, or somewhere like that where we could do population-based studies like in the Bahamas or some place like that – if I wanted to do that I'm sure we could find some volunteers amongst you who could help us with the field work!

But it has not been systematically studied. If you take Italy as a bit more south than we are, the population prevalence in Italy is more or less the same as it is in Norway. So they are pretty big distances apart. That's the best example I can give you, because – San Marino is another place where they went around the place and knocked on everyone's door. They got a somewhat lower prevalence than Charstead did, who went around Norway knocking on peoples doors' – not really mind-bogglingly different, so I think that there may be a little bit in the latitude question, but we don't have equatorial data – that would really be quite interesting. There is almost certainly something in the timing of the onset of the episodic bout, I suspect, with the night and day lengthening and that would be a fascinating question in the northern and southern hemisphere and all sorts of interesting things like that and there will be some fascinating biology behind that, but I don't think people in the UK are significantly disadvantaged by being born here in comparison to Italy, for example, although some days when it's raining we might think differently?

"What about when people move from one climate to another and come to temperate zones? Is there any evidence, is there a higher proportion of those people who suffer from....."

That's a really, really good question, and no-one has systematically looked at that. That is where you are really doing a systematic population-based approach to things, because you could get at that problem from people who have migrated, but no, there is no data for that at all. The migraine people have looked at that a little bit and it is clear that in migraine for example, that you carry your risk from whence you come, so the population risk of the Japanese for example, in Japan, is about the same as it is in the US and it less than the Caucasian Americans, so I suspect if there is a population risk you would carry it with you, but it hasn't been done. It's a very good question.

"Can you read anything into the changing nature of attacks. I would go about seven years, spring/summer and have eighteen months and then seven months, then eighteen months and back to spring/summer again. Is there anything you can read into that."

Not really, the only pattern that seems to make sense is the lengthening pattern. In general terms, longer attacks, generally, will bring about longer interbout intervals, generally speaking. Longer bouts, generally produce longer interbout intervals. In general terms that seems true, but in general terms I can't tell you anything constructive about the variability that you talk about. It doesn't point me anywhere. It points me to the brain. This brain area that's here, one of the things that's close to this is something called the supra-chiasmatic nucleus. It is an area of the brain that is the thing that gets you up, so to speak. It regulates your daily rhythm or circadian rhythm, so if you put humans in a cave – you take a group of people and put them in a cave as has been done, they cycle at about 25 hours, little bit around there. If you were out in the sun, you tend to shift yourself one hour. It's the sort of thing people often find when they go on holidays for example. They have a bit of a break and they get up a little bit later every day and then they stop doing that. That's normal, that is this body rhythm and mammals, most species on the earth, are regulated to a 24 hour clock by the sun. That is how we evolved, or God meant it to be, or whatever you prefer.

So this area that I have illustrated on the slide, is actually close to that clock region and that's one of the interesting bits of biology around the disorder, the way it can vary with this changing in the exposure to light, so around the autumnal and the other equinox, you get a change in the amount of light that you are exposed to. You'd think it was relatively trivial, particularly with the amount of cloud we get, but it does seem to drive changes in the disease, so that is the sort thing that tells me that we are in the right place to understand what the nature of the problem is.

One of the reasons that this is all a bit limited in this area, is pathology. As I think I said in 2005, I don't expect anyone to throw themselves under a bus this afternoon – in fact it would be quite unhelpful as it would only mash your brain up! But there will come a time when your brain will be more useful to us, than it would be to you! Not to encourage anything radical, but there will come a time, when looking at the pathology of this area, there is only one way you can go that and I hate to be gory, but it is actually getting the brains! We have two we are working on now, one in particular we are doing some detailed histo-pathology on and it will be the first time that has been done and again it just points to this area and that will be kind of exciting. It is a bit weird in a way, because I have the Order of Service of the guy who gave me the brain sitting on my desk – it's one of my daily memories that there is a reality to this and you have to do something about it. It's quite slow pathology, but it is quite a serious business to be able to get a look into this.

"*Verapamil – how safe is it for long term use?"*

Well, we are in relatively uncharted waters. It's been used in this kind of high dose probably for more than ten years now. A lot of the issues that have emerged, the ones I have mentioned to you – the constipation, leg swelling, gingival hyperplasia to the gums, so dental hygiene is important. The heart, you can monitor that and you can know that and then there is the question of whether it alters the disease long term, that's an unanswered question and I don't really see a lot of convincing evidence for that, although I understand in individuals that they will have had that experience, but in a general sense, I think there is no bad news long term – there is no really consistent bad news long term in the verapamil story.

"I'm on 720[mg] and I saw my doctor on Tuesday and..." (cannot hear rest)

Well you know, safe and comfortable that I wouldn't put in the same paragraph there. You could stop taking it and the worst thing that could happen is that your attacks could just go bonkers and that mightn't kill you, but it may tempt you to do that! So while it's not dangerous if you put danger as in life-threatening, but in general terms we don't suggest people do that because you see people who do that whose attacks just get unleashed and that is just horrible. It's alright for someone to say

in the comfort of their own seat, because that's not dangerous, but dear me, if you let someone's cluster headaches go completely uncontrolled and they are having many a day, that's a bad business, that's very unpleasant, I don't have to tell you that! If I was you, I would be doing everything gradually. There is no point, it's not like a race. What is the worst thing that can happen, you know, have a bit of constipation for a little bit longer, we don't want to talk about your constipation in depth here and in public! But you know, that is the worst it could be – but the worst of rushing is that you could have many really horrible attacks. Information is everything!

Are we pretty much done? We've got some pretty personal topics out!!! No-one has talked about sexual activity and I had a guy come to me on Friday who told me that he used orgasm as a therapeutic approach – I don't think we'll ever get it in the BNF, but I can't advise against it! In fact I could think its probably a perfectly reasonable thing to do. I'm not going to ask how many people use that approach, but he said to me "Well why don't you ask them all?" And I said "You don't really think that a whole lot of people are going to talk about their orgasm in public?!!!" I mean, OK what can you say – he'll ask me next year whether I asked and I'll just say I drew your attention to it and I can say that honestly without getting myself into any trouble!

I thank you for your observations and again thank you for your involvement. It's not easy, this is never going to be easy, but it is better than it was and I am sure it will just – if we all sort of stick together and push forward as opposed to trying to push outwards, and understand that the problem is ignorance and the problem is lack of funding and the problem is lack of understanding. None of the problems are in the room – all the problems are outside the room, so when we leave the room if we are going to get together to sort the problems out.

Thanks very much