

HSF Patients' Day



Wednesday 15th May 2013

Hughes Syndrome Foundation Patients' Day 2013 Wednesday 15th May 2013

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Chairperson (Professor Graham Hughes): Well, we're going to open with me and it's something different, and I hope it works because I haven't actually seen it.

A month ago the World Conference on Lupus was held in Buenos Aires and they had 1,500 doctors there and patients with lupus, so it was a big meeting. I was asked to give a ten minute presentation in the opening ceremony, and there was no way I was going to fly fifteen thousand miles each way for ten minutes, so they said, "You could give a video". So up in the lab here we did a little video. The title they gave me was 'Anticardiolipin syndrome in 2050'. They asked me to guess what would be happening in the future. So this is the presentation. The first few slides are thanking various people of course who were involved, but then it's my guesses for what's going to happen in the future.

Professor Graham Hughes **The future: Hughes syndrome in 2050**


Graham Hughes: This is Graham Hughes speaking from London, and I'd like to thank the organisers for allowing me to present at this distance for the conference. It was 30 years ago that we described the antiphospholipid syndrome in clinical detail, and our first papers were in the British Medical Journal and Lancet in 1983. But a couple of years later our first paper across the Atlantic was in the International Lupus Conference in Canada, and I'd like to pay tribute to my two colleagues, Doctor Nigel Harris and the late genius Doctor Aziz Gharavi, who between them really were the brains behind the setting up of our antiphospholipid testing. It also gives me the chance to pay tribute to Marvin Fritzler who I'm sure has been mentioned already in this opening ceremony, but he was the inspiration behind the series of international lupus conferences at which we first presented our data on antiphospholipid syndrome.

That was published in the Journal of Rheumatology, and it also gives me the chance to pay my own homage to the late Duncan Gordon, who after the journal was set up by Metro Ogryzlo, for so many years built up this superb international rheumatology journal, the Journal of Rheumatology. And finally in my pictures of honour, I'd like to show Doctor Munther Khamashta who is my colleague over many years at St Thomas' Hospital, and who really with me set up the London Lupus International Conference which many of you attended, and for which I am so grateful to Munther.

So, what are the predictions for 2050? It's not that far ahead, but I'm going to make some fairly strong predictions and, well, we'll see. The first is that of course it'll be the first intergalactic conference on APS and it'll be held in the Disney Conference Centre on the moon, so start booking your tickets now with Virgin Atlantic to get your place in this meeting!

What are the predictions? Number one, antiphospholipid testing will become worldwide. Not just confined to major hospitals but it'll be available to general practitioners, surgeons and lay people, and over the counter kits will be available and the kits will be simplified, will be a single test for antiphospholipid family of antibodies, and we'll do away with the horrible lupus anticoagulant test.

What about the clinical features? First of all, I think there will be new hope for migraine sufferers. For me, migraine is number one or maybe number two feature of the antiphospholipid syndrome. Almost invariably you get a history of migraine as a teenager often going away but coming back in their 20s and 30s, and often familial interestingly. Migraine is a major disease worldwide and the cost is huge. This is several years ago, an estimate from the States of \$17bn spent annually on this disease. I have thought for a long time that antiphospholipid syndrome is a major link with migraine in general, and a few weeks ago in Nature a major paper appeared on a large series of migraine patients linking migraine statistically with stroke. Of course they didn't measure antiphospholipid antibodies, but my prediction is APS will be the major missing link between migraine and stroke.



My next prediction is stillbirth, late pregnancy loss. And this was in the London Times several weeks ago, the stillbirth scandal. 'Every day as many as three babies are stillborn who could have lived. It's time for the NHS to adopt new policies and a new attitude'. We know now that one in five cases of stillbirth the mother is aPL positive, and this is from ((large ?)) series including the very recent collaborative studies from ((Mike Glocshun ?)) and colleagues here in the United States. Testing more frequently in early pregnancy, and my hobbyhorse is to test after one, certainly at the moment after two miscarriages, not the dreaded three miscarriages, and in that way we might avert what The Times describe as the greatest tragedy that can befall a family, that of late pregnancy loss. Stillbirths will be cut by 50%.

What about the predictions for the cardiovascular system? Well, a recent paper not so long ago by ((Recco ?)) showed that antiphospholipid positivity was present in 40% of their cases of acute coronaries. And there are a number of papers now appearing linking coronary disease, including other features of cardiac disease, with antiphospholipid antibodies. Therefore my prediction is that young heart attacks will be reduced, especially in women, and there will of course be protection against stroke. There will be testing in early TIAs and certainly in young people with abnormal neurologic features.

I think that in addition the antibody will be involved much more and reflected in the accelerated atherosclerosis seen in many diseases such as lupus, and the prediction here is that antiphospholipid syndrome a crossroads of autoimmunity and atherosclerosis, as defined by Yehuda Shoenfeld in this paper, will become recognised widely, and antiphospholipid antibodies will become recognised as the major cause of accelerated heart disease in lupus.

What about lupus? One of the major problems of antiphospholipid syndrome in lupus and in primary APS is memory loss. It's now becoming widely recognised, and for me it may be the number one feature of the antiphospholipid syndrome. By testing more widely I am sure that some cases of memory loss will be treatable, not some but many, and this slide from our unit some years ago shows the very dramatic effect of a short trial of heparin, we used 10,000 units of low molecular weight heparin. The improvement in this case of memory scale, word finding, from thirteenth percentile to eighty-fourth. And we see this more and more. This morning I saw a patient who has now been five years on low molecular weight heparin. She couldn't tolerate warfarin and found heparin very much better, and she has been free of what she calls brain fog and doing extremely well. I should add that she's married to a haematologist!

And finally, what about the rest of lupus? I think the antiphospholipid syndrome has had a major impact on SLE. Certainly it's now recognised as probably the major cause of chronic disease or chronic damage in SLE. But in the renal biopsy I'd like to pay tribute to Mary-Carmen Amigo's work in looking at the microthrombotic lesions of SLE, and this has really revolutionised our thinking in lupus, in lupus nephritis and the interpretations of lupus biopsies.

So in summary, I'd like to thank Mary-Carmen Amigo, Bernardo Ponsistel and the organising committee for allowing me to take part, at least from a distance, in this meeting. I'd like to wish you a very successful lupus conference. Thank you very much.

Chairperson (Professor Graham Hughes): Well, I hope some of those predictions come true. These are my predictions and I'm sure you have your own, so perhaps we can come back to that a bit later on. I'd like to move straight on and welcome Beverley Hunt who's going to talk about her experience with the old versus new anticoagulants. Professor Hunt is Professor of Haematology here. One of the Lupus Team, Beverley.



Professor Beverley Hunt

Old and new oral anticoagulants for Hughes Syndrome

Beverley Hunt: *Okay so I look in the audience and I see lots of people who are on Warfarin and a few on a few other things, some on low molecular weight Heparin and others and what we're going to do now is I've got some slides just to update you where we are with all the new oral anticoagulants and then it's question time and I will answer anything which is a legal question with a legal answer.*

Okay so what are we looking for with an anticoagulant? We want something that is efficient, effective, safe and convenient and when we look at Warfarin and they're all of the Warfarin-like drugs called Coumadins, we know they work and we know they work in Antiphospholipid Syndrome without a doubt. The trouble is we have issues around safety so we have a drug that if we all take 10mgs we all get different blood thinnesses and then, depending what we eat and drink and the medication we take in the next twenty-four hours, will have a different result the following day.

So there's a lot of problem with control and there's a lot of problem with bleeding and we estimate probably we have a bleeding rate as high as 1% – 2% per patient year so not particularly safe but the best we have. It's reversible so we can, if you have a big bleed, give you an injection of Factors II, VII, IX and X which are the ones that are missing when you're on Warfarin and can reverse it immediately or give you Vitamin K. And lastly, not very convenient, people are tied to anticoagulant clinics and regular monitoring and about the same time that Warfarin came along, Heparin came along; a medical student discovered Heparin in Baltimore at John Hopkins Medical School and it gradually reached practice in the Second World War.

Again if you have an infusion of Heparin it really does thin your blood but like Warfarin absolutely useless as far as getting a steady level going and if you were to put someone on a Heparin pump, quite a lot of the time they'd only be in the right range and that would be because they'd be going from under-anticoagulated to over-anticoagulated, very difficult and some nasty side-effects. If you had daily injections of old fashioned Heparin all the way through pregnancy as we used to do, you had a 2% risk of fracturing your vertebrae at the end of the pregnancy because they were so thin, osteoporosis.

Again, not very convenient; injectable and so when the new low molecular weight Heparins – they're not new anymore but they were when they came in in the '70s, came along they were a major advance because for the first time we could give an injection, we all got 5,000 units of low molecular weight Heparin such as Clexane or Fragmin, we'd all have the same blood level so highly predictable. Good effects, again not convenient because we want tablets.

Now the other one that lots of people don't know about is Fondaparinux and there are some people in the audience who are taking it. This is like Heparin but it is synthetic, it's produced in vats because even in 2013 we're reliant on getting Heparin from pig mucosa and most of the pigs are in China. So this is pig-free, that's why the little pig is up there, it doesn't have any of the side-effects of Heparin, it's just a tiny little part of the Heparin molecule that works produced in vats. It's a really nice drug and in medicine we used it in all the areas we'd use low molecular weight Heparin and we'd replace the Heparin with the Fondaparinux but it's terribly expensive so it doesn't get as widely used as it should be. So those of who are on it, you're very lucky because of the expense.

So where are we now? We now have this amazing time when all the big pharmaceutical companies have realised there's a big gap in the market. There are over a million people in this country, in the UK, on Warfarin. Probably should be one and a half million but some of the GPs are very scared at prescribing the Warfarin because of the high risks so you can imagine the size of the worldwide market. So we've got these new drugs coming through to replace Warfarin and the wonderful things about them are they have a predictable anticoagulant effect so that if we all

took the same dose, we'd all get the same levels, not affected by food, not affected by alcohol, not affected by many other drugs as Warfarin; fixed dose so whether you weight 50 kilograms, 150 kilograms, the same dose, no need for monitoring, no need to go to the anticoagulant clinic you can rip up your anticoagulant book. What a lovely feeling that must be.

So we've got two types, we've got direct thrombin inhibitors and it's called Dabigatran it's the only one and basically it just binds to thrombin, it inactivates it and then we have got Rivaroxaban which is the first of very many direct anti-Xa agents which basically means it binds to activated Factor X and then these magic words predictable anticoagulant effect, fixed dose, no need for monitoring. Yay.

So where have we got to? Well there've been tens of thousands of people worldwide put into clinical trials, we've done a lot of them here, we've been part of them and what you can see across the top is Rivaroxaban, Dabigatran, Apixaban, Edoxaban. They're all abans and all the clinical trials they're doing and whether they're licensed or not and where they all start off is they try them in orthopaedic surgery after hip or knee replacement, got about a 50% risk of a DVT after hip or knee replacement so it's a good place to try out a drug and they compare it with standard treatment. They all pass with flying colours, they are all licensed apart from Edoxaban in the UK and we're using them.

The next one is stroke prevention and atrial fibrillation. Now if you go to your anticoagulant clinic with Antiphospholipid Syndrome you know you're a very special patient because you're about half the age of the whole clinic and the clinic is full of very old people who have atrial fibrillation and we're trying to prevent them from having a stroke. That is the big market. 80% of the anticoagulant clinic is those patients. So these drugs have been tried out there and the big news about these new drugs is not only are they as good as Warfarin, they have a much lower bleeding risk and the real worry when you're on Warfarin is you have an intracranial bleed and they cut the intracranial bleed by half. Wow. So they're starting very slowly to be taking up. And then the last row at the bottom is treating deep vein thrombosis and pulmonary embolism and of those Rivaroxaban is the only one so far to have a licence. Now if you were to come here, to our emergency department, with a new DVT we would treat you now with Rivaroxaban, we wouldn't put you on Heparin and Warfarin, we'd just put you on Rivaroxaban and I think we're probably one of the first hospitals in the UK but others are quickly following us.

So exciting times. It all sounds marvellous doesn't it? But there is no drug without its problems and the bad news here is we don't have an antidote. So there we have been working on all these new oral anticoagulants for ten, fifteen years each big pharmaceutical company must have spent five billion pounds; it says it's about five billion pounds to get a drug to market. There is no specific antidote so if you look in the big medical journals they're full of stories about people who bleed on these new drugs.

And when we look at the advice given on how to reverse these new drugs, it's all old fashioned stuff. You might not think this is old fashioned, to me it's old fashioned, it's just saying "well if someone's bleeding, stop giving them the drug, perhaps give them a bit of activated charcoal to take out what's left, well you know make sure ((?)) of care is ready, check their blood pressure" I'd be doing that anyway, there's nothing specific there for me to be able to know I can reverse this particular drug and all we have is one paper, one paper reversing Dabigatran and Rivaroxaban. A group of healthy men, they were given these drugs and then we tried to reverse them with the drugs we'd normally use to reverse Warfarin and Rivaroxaban seemed to be reversed but Dabigatran didn't.

So we have this incredible situation where we have these drugs being prescribed worldwide but we don't have an antidote and we don't really have very good advice on how to reverse them. And in the States the FDA, who are like our Medicines Control Agency here, they're in charge of all the drugs, were so worried about all this that they did their own private investigation and they thought that perhaps the trials were wrong, there are so many reports of bleeding

on the new drugs, was it that they had a higher rate of bleeding after they had been licensed compared with what was going on in the trials?

So they managed to get all the data from the insurance companies and I've got the slide missing but basically the rate of bleeding is very low, it's just that every time someone's bleeding, a doctor says "ooh I've never seen this before" and is writing this up and sending it off to the Journal and the Journal's saying "ooh we've never seen this before, we've never published on this before, we will publish" whereas of course if somebody comes in and they're bleeding on Warfarin, yeah it's old hat.

So what have we got coming through? We actually antidotes so we've got an antidote coming through for all the anti-Xas by a company called ((Protola?)). I'm afraid it's not on the share market I don't think but if it was I'd be advising you all to buy the shares. And then we've got another one coming through to reverse Dabigatran but they're all about five years from getting out and getting a licence and being available. So in the meanwhile, we are using what we can and I've been all over Europe in the last two months talking to other doctors, lecturing at conferences and we have a plan on how to reverse the new oral anticoagulants it's just not very tried and tested.

So then we come to you because you want to know whether the new oral anticoagulants are of use to you and one has to say there have been no trials specifically looking at use in Antiphospholipid Syndrome. Now when you do a trial and you randomise ten thousand patients with deep vein thrombosis as we've just finished with Edoxaban, you know there must be about 10% of them that must have Antiphospholipid Syndrome 'coz that's the data that we have from previous work but we're not looking at them specifically and we're just treating them in the normal way and they seem to be doing fine but we haven't actually analysed that data separately. And then the other key thing to say is that all of the tens of thousands of patients that have been using the new drugs all have conditions where they run their INR between two to three and there are many, many Antiphospholipid patients who are running their INR between three to four and I don't know and no-one knows what dose of these new oral anticoagulants we have to give to get the same blood thinning effect.

So to start to answer these questions, we are starting a study here and at University College. It's funded by the Arthritis Rheumatism Council, they've given us about £200,000 and we are going to randomise 156 patients who've got Antiphospholipid Syndrome to standard treatment Warfarin versus Rivaroxaban for six months and we aim to show that Rivaroxaban has the same effect, the same anticoagulant effect as Warfarin in Antiphospholipid Syndrome and we're being very, very cautious here and we're only asking people to enter if they've only had one blood clot, either a DVT or a pulmonary embolism, we can't take on anyone with arterial problems 'coz they're running higher INRs.

So the patients have to have a target INR of two to three and been on Warfarin for at least six months and the problem with all the new oral anticoagulants is that they are teratogenic, they cause foetal abnormality in animals so we have to make sure that if you're fertile you use contraception and we can't take anybody who's running a higher INR or had an arterial event, by that I mean heart attack or stroke or if they've got any particular problems such as renal or liver impairment, pregnancy, breast feeding or taking one of the very few drugs that interferes with Rivaroxaban.

So lastly we do have some data on reversing Rivaroxaban and it's actually, apart from giving Vitamin K, we will probably give and have given the prothrombin complex concentrate that we use when we reverse patients on Warfarin.

So there we have it, so we do have a new age coming, we do have new oral anticoagulants, so it will be much sexier, more convenient than Warfarin and free up people from being attached on a piece of elastic to the anticoagulant clinic but we have still got difficulties and if I had Antiphospholipid Syndrome, I'd be quite happy, if I was running an

INR of three to four to let us over the next few years, learn more about the new oral anticoagulants so that eventually we'd know what the right dose is we can try it out in Antiphospholipid Syndrome.

Thank you very much.

Chairperson (Professor Graham Hughes): Thank you Beverley, any questions or comments?

Q1: The final phrase on that slide - so studies in APS are starting?

BH: This month. So we've going to start the rat study we hope at the end of this month.

Q2: Are you going to have enough money to see it through?

BH: Absolutely yes, we absolutely have.

Q3: I've been trying to get on the synthetic Heparin because it's got a much longer half life, I'm currently on Tinzaparin, because it's half life is so short in a hour and half's time I'll have run out of Heparin because my trough goes down to .01 by 24 hours so I've got no cover because I've got a trough test and a peak test and Xa test. I've been trying to get on the Board-

BH: Fondaparinux it's not the most user friendly name.

Q3: -my GP's quite happy for me to be on it but unfortunately it's red on his screen so it means he can't actually prescribe it. How do we actually get it prescribed if the GP can't actually prescribe it? I know you prescribe it because I've seen other people talking.

BH: Okay I think the first thing to say is that just because you've got a low trough level of a low molecular weight Heparin doesn't mean to say it's not having an effect and we don't know with a low molecular weight Heparin whether it's the height that's important or the trough that's important but you haven't had a recurrent event so it's obviously working. I don't know enough about you. If you want to get hold of any drug then your GP is supposed to follow the guidelines given by their Primary Healthcare Trust or it's now known as their CCG Clinical something Group and some GPs ignore the advice and the other thing is to ask the Consultant in the hospital if they would prescribe it for you.

Q3: I asked the Consultant where I've been at my local hospital and she said she's never prescribed it before and therefore she wasn't prepared to prescribe it now. She appreciated my trough level is 0.01 after 24 hours and she said I didn't have any cover and my peak was .57 but I'm still waiting.

BH: So the other thing is to get yourself referred to someone who will prescribe it.

Q3: I'm seen up here but I'm not sure whether all your other Consultants-I'm under Dr Davies.

BH: Obviously I can't discuss you and your individual needs but you'll have to see me afterwards.

Q3: Thank you.

Q4: What research is not being done that should be?

BH: Well obviously we need the antidote don't we and we need to speed it through. Having said that, we're using a

lot of Rivaroxaban here and we haven't had anybody bleed on it because there is a lower bleeding rate with the new oral anticoagulants. It would be nicer to do clinical trials much more quickly, it's taken us nearly two years to set up the study, the ((rat?)) study although we had the design and we had the money the bureaucracy around doing clinical trials these days is truly unbelievable and the man hours that have gone into this study – we meet for an hour and have to jump through some other hurdle – it's amazing so I'd like to make sure that the EEC, they're about to review how they do clinical trials, reduce the bureaucracy there.

Chairperson (Professor Graham Hughes): *Can I throw in a couple? I think research is not being done adequately in other departments, the world of multiple sclerosis, the world of migraine, the world of heart attacks are very slow. We've quoted two heart attack studies, there's only about five major studies so I look at it from the other angle if you're a doctor looking after patients with memory loss, what percentage have this treatable condition?*

Q5: *Does Warfarin actually reduce the ability to work after a long period of time?*

BH: *It shouldn't do no. So the question was does Warfarin lose its ability to work over a long period of time and the straight simple answer is no.*

Q5: *Okay. I've been on it for forty years and it was quite steady. Now over the last year or so it's fluctuating.*

BH: *There are so many reasons why some individual has unstable INR from time to time, ageing, change of drugs, change of diet, alcohol, so many things it will be difficult to comment on what it is in you. We would need to sit down for twenty minutes and work through it all.*

Q5: *Okay thank you.*

Chairperson (Professor Graham Hughes): *Last question*

Q6: *So we had patients on Warfarin for forty years or fifty years and we know that you don't get any long-term issues with Warfarin. What about the new drugs? So if we're lifelong patients and these drugs have been around for only five/ten years, do we know what happens to the liver or the kidneys or any other organs?*

BH: *So the question's all about we've had Warfarin for fifty years and we know it's safe if we take it for fifty years but we don't know the safety of the new oral anticoagulants and I can't guarantee that after ten years on Rivaroxaban you won't turn green because we don't know the answer but looking at how it works and seeing the patients who've been on it two/three years now, they all seem to be fine thank you very much but of course that's no guarantee for the next ten years. Thank you.*

Chairperson (Professor Graham Hughes):

Our next speaker is Doctor Anisur Rahman from University College Hospital, who spoke here before and is known to many of you, and is going to talk about some of the newer research on the antiphospholipid syndrome.



**Professor Anisur Rahman:
Domain I, the hidden face of antiphospholipid syndrome**

Hello. It's always a pleasure to come and speak at the Hughes Syndrome Foundation and this is my third year here, and thanks to Graham for introducing me.

Now the last two years, what I did was I came and I talked about the research we're doing at UCLH, and that was fine, but this year I'm going to do something different. And the reason I'm going to do something different is because of what happened after last year's talk. So after last year's talk, I went back to the unit where I work, and one of my younger colleagues, who's very adept with social media, she said, 'Did you know that Hughes Syndrome Foundation has a Facebook page, and on that Facebook page they're talking about you?' So, being as human as the next guy, I obviously had to go and look at the Hughes Syndrome Facebook page, and there was something about me, but it wasn't very much and that wasn't the interesting thing. There was something much more interesting on that page, and having read it, that has changed the talk I'm giving this year.

So what did I find on the Hughes Syndrome Foundation Facebook page? Well, the first thing was, there were lots of people from the West Country; there was all this stuff about, 'Oh I came up from Bristol or Somerset,' and I was very pleased because I myself am from the West country, I'm a Bristolian and a very proud Bristolian. Anybody here from that part of the world today? Great stuff! So yes, I'm a Bristolian, and in fact I'm still a Bristol Rovers' supporter, and anybody who knows anything about football will tell you that only a Bristolian could possibly be a Bristol Rovers' supporter. So I'm very fond of that part of the country, so that was good.

But what wasn't so good was I started reading the Facebook page, and also the blogs, and I saw that actually people were not very happy. There were lots of quite sad stories on that Facebook page and I started reading through them. And the sad stories, well basically they fell into two types: there was one sort of narrative which said, 'I was not treated well in the hospital where I am, and I really only felt I got the right treatment when I went and saw Professor Hughes or Professor Khamashta or somebody at St Thomas's or London Bridge.' That was one type of thing, people who were not happy with what had happened. And the other type of thing was to do with seronegative antiphospholipid syndrome, which is antiphospholipid syndrome which always tests negative, and people were saying, 'Well, why is it so hard for me to get the diagnosis? Why is it that the doctors won't make this diagnosis without the tests?'

So I felt quite sad reading these stories, because, as a doctor, I don't like to read stories about people being dissatisfied with doctors. So what I thought I would do in this talk is try and address some of those things. And before doing that, I should explain who I am and why I should address this. So I'm a bit unusual in a speaker at this meeting because I have nothing to do with Thomas's. I don't belong to St Thomas's at all; I belong to University College London and I've never trained here, not in rheumatology, and I've never worked for Graham or Munther. But that doesn't mean that I disagree with them or that there's arguments between us. In fact, I see them as very valued colleagues and we've done a lot of work together, our unit and their unit, and I think that's the way in which medicine should be. I think people who work in different units should be able to work together. So that's why it was sad when I read stories saying, 'My doctor said they just don't agree with that so they're not going to treat me.' I don't think things should be like that.

And what worried me about this was that if it were really true, that the only place that you can get proper treatment for this syndrome is here, then that's not good, because the vast majority of patients in this country aren't going to come here. What about people who live in Inverness or Aberystwyth or Anglesey? They're not going to come to St Thomas's, and Graham can't go on forever, although I'm sure he's trying to! So there has to be a better way, there has to be a better way to do things, so that's what I was thinking. And with me, because I'm not from St Thomas's, the way I look at things is: let's see what the ideas are coming out of St Thomas's, and let's see whether you agree

with them or not, and that's how science should be. So, for example, if I'm giving a research talk or presenting some research, and Graham comes and watches, he might not agree with everything I say, and he might come up to me afterwards and say, 'Why did you say that? What were your reasons?' And I would expect us to be able to have a discussion about it, and that's fine, as far as science goes. But when you put a patient in the scenario, when there's a patient, and we're talking about the patient, then we should both be trying to do what's best for the patient, to the best of our ability, and I think that's really my starting point.

So what I'm going to try and explain is why some of these things are so controversial, and why sometimes doctors disagree, even though they may have the best interests of the patient at hand, and why I think these things are going to get better. In fact I think the future is going to get better, and I think there will be broader agreement about some of the things which are bothering the people on the Hughes Syndrome Facebook page. And after I've finished talking you can tell me whether I've convinced you or not.

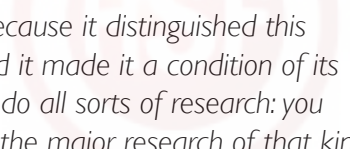
So, why is it that seronegative antiphospholipid syndrome appears to be so controversial? So one thing is to do with the history of a syndrome and the definition of a syndrome. There's a very clear definition of the antiphospholipid syndrome, which I'll tell you, and because of the way it was defined, some people feel that you absolutely cannot diagnosis it without a positive test, because it was defined that way in the first place. But my argument is that definitions can change over time. Just because something was defined one way in the mid-80s, doesn't mean that it always has to be defined that way, and I'll show you some evidence to support that.

And the other thing is the implications of diagnosing APS. So doctors, many doctors, in general, are worried about making this diagnosis because it has a really big effect on what you do for the patient. If a person comes into a hospital with a clot, they'll go on to Warfarin probably, and they'll go on to it for between three and six months. But if that patient has antiphospholipid syndrome, then essentially the evidence, which is fairly undisputed, is that patient has to go on Warfarin forever, there's not really a safe time. So you can see that label, APS or not APS, makes a really big difference, so you've got to be sure. And that's the thing: how are you going to be sure, and how are you going to be sure if the tests are negative? So that's why many doctors may have difficulty with this idea of seronegative APS, because they're thinking: 'I don't have the comfort of the test. On my initiative, am I now going to commit this patient to lifelong Warfarin?' Tricky.

Now if you're Graham Hughes, you have the benefit of 30 years' experience of seeing lots and lots and lots of people, and most of us, myself included, do not have that. I can't say I've seen 30 years' worth of APS patients and lots of them are seronegative. So you can see that it may be difficult for some doctors to make that step, because the treatment, as Beverley has expressed so cogently, is not without side-effects. And I personally, if you said to me, 'Take Warfarin for the rest of your life,' I wouldn't be very keen on the idea! If you said, 'There's very good evidence that it will save you from a stroke,' I'd do it, but I'd wish that there was something better. So this is where I think people have this difficulty, this mental difficulty, in putting people on lifelong Warfarin when the tests are negative.

Okay, so I want to tell you about the definition of APS, and I guess some people may know it and some people may not. But back in the 80s, and this was before I was active in rheumatology, and I'm from a kind of a different generation than, say, Graham is, so for me this is history, these are things I've read about; I wasn't involved in these things at all. But what it was defined as was you can be said to have APS if you have a clinical thing, such as a stroke or a clot, or miscarriages of certain kinds, and a positive blood test. You had to have both. And furthermore, the blood test can't be positive just once, it has to be positive at least two times, and they have to be separated in time. And the reason that's important is there are some infections, some viral infections, where those antibodies go up for a little bit, and then they never come back again, so that would be misleading, and that was how it was defined.

In the very beginning, this syndrome was defined as you have to have a blood test positive, and you have to have a clinical event, and if both those things aren't true, you cannot be said to have the antiphospholipid syndrome. And



at the time, when that was done, I think that was great, that was a great definition, because it distinguished this syndrome from other causes of clots and for other things which caused antibodies, and it made it a condition of its own, something separate from all other conditions. And with that definition you could do all sorts of research: you could find out what happened to people with those conditions, and certainly some of the major research of that kind was done here at St Thomas's and there was a very famous paper by Professor Khamashta, who I think many of you will have met, in the mid-1990s, where they described their experience of all the people who had fulfilled that definition for the last ten years before that, and that was a seminal paper which was published in the best journal in the world, which completely altered the management of this syndrome. And the point I'm making is, without a definition you couldn't do that work. So it was very, very important to have that definition at that time, and I don't dispute it at all. The definition was changed over the years, it was modified in small ways, but always maintaining those two points: you have to have a positive blood test, you have to have a clinical event. So, if you believe in that definition, and if you are not ever willing to change that definition, you cannot have seronegative APS; it is impossible, because the definition says you have to be positive.

So the question is whether we're willing to say, 'Let's change our definition now, let's be more flexible and allow there to be seronegative APS.' And, actually, in many ways that shouldn't be hard because there are other diseases in rheumatology, like rheumatoid arthritis and lupus, where everybody accepts that you can be seronegative, that the blood tests don't have to be positive. They're positive in the vast majority of cases, but some people are negative. It's only APS where people have this mental block, I think, and that's because of the way it was defined in the first place. In a way, it's an accident of history, in my view.

Okay, so there has to be a positive blood test, but what do we mean by blood test? What does it actually mean? So in the beginning what it meant was two things: there's a blood test called the anticardiolipin test, and cardiolipin is a sort of phospholipid which you get out of ox heart muscle. Now why it is out of ox heart muscle, I really don't know, perhaps when we had an ox heart on a shelf and decided to mash it up. I don't know why that is. But you can get cardiolipin, you can use it in a test in a laboratory, and you find that it's positive in a lot of patients with this syndrome. It was useful, but not in everybody. And then there's the lupus anticoagulant test, which is a completely different sort of test altogether and works in a different way, and that's also useful. So the original definition said, 'You have to be positive in at least one of these tests, because they test for these antiphospholipid and antibodies,' but it was well known from the very, very beginning that not all patients with APS would test positive for both of them. So some people would only test positive in the cardiolipin test, other people would only test positive in the lupus anticoagulant test, so you could have patients who were seronegative, who tested negative for one of these tests, and we've always known that, but the definition said you had to have at least one. But things that didn't stay that way, that was the original definition.

But then in 1990, some groups found that this whole cardiolipin thing was a bit of a red herring, and what they found was: if you took blood from the patients who had this syndrome, we knew they had the syndrome, they fulfilled the definition of a syndrome, and if you took their blood and you purified it very, very rigorously, so you got the antibodies out, they didn't bind cardiolipin anymore. Actually, what they bound was a protein called beta-2 glycoprotein 1, which sits in the blood and attaches itself to cardiolipin. So the cardiolipin test was actually helping us, but the antibodies were not sticking to cardiolipin itself. So you can see, it's all getting a bit complicated now: we've defined the syndrome as being dependent on this test, but now we find out that the test is actually not telling you exactly what you thought it was telling you. Actually what it's looking for is these antibodies which bind beta-2 glycoprotein 1.

So what is this beta-2 glycoprotein 1? Well, we all have it, all of us have it, it's a normal thing in every human being, and we don't exactly know what it does for us. It may do lots and lots of different things for us: it probably is involved in clotting and preventing people from clots. One reason why we don't know exactly what it does is that there can be mice who don't have it at all, they lack it, they don't have it, and they're completely healthy, they seem to get on quite well without it. So we don't know exactly what it does, but it's something to do with clotting. But what we do

know is it's very, very critically important in the antiphospholipid syndrome. The antibodies which cause this syndrome cause the clots and the miscarriage, and they attach on to this thing, this beta-2 glycoprotein. Well most of them do, not all of them, but most of them do. And it's actually a bit clearer than that, because beta-2 glycoprotein 1 is a protein which has five bits, five domains, which are a bit like beads on a string, and of those domains, domain 1 is the most important. So when they discovered this about beta-2 glycoprotein 1, some enterprising scientist invented a brand new test, which was called the anti-beta-2 glycoprotein 1 test. So now there were three tests instead of two tests, so you can see the definition has changed over the years and it hasn't been unchanging. In the beginning there were just two tests which could be positive, and now there are three tests which you can use, but still you have to be positive in at least one of them to be counted as APS under the current definition.

Okay, so here's a picture of beta-2 glycoprotein 1 and it's got five domains. Now ordinarily it circulates in the blood, domain 1 sticks to domain 5, so it looks like a circle, and most of beta-2 glycoprotein 1 looks like this. But, sometimes beta-2 glycoprotein 1 attaches to the surface of cells. Now the surface of cells have these phospholipids, and so when beta-2 glycoprotein 1 attaches, it attaches by one end, by the domain 5 end, and the other end, the domain 1 end, sticks out and the antibodies can come and attach to it. So this is how we think antiphospholipid syndrome works: you have these antibodies in your blood, which don't touch the ordinary beta-2 glycoprotein 1, the circular form, but if it's attached to cells, they can attach to it by domain 1, and this causes all the problems; this is what we think is going on.

So what has all this got to do with the seronegative antiphospholipid syndrome then? So this is my view. You can see, I hope, that our ideas about what the antibodies are have changed since the original definition. So why, then, do we have to stick to the original definition? Why do we have to stick to the original tests? Or to put it another way, is it possible that there can be people who really do have antiphospholipid syndrome, but they don't test positive in the tests we have already, but if we invented some new tests, like a test for anti-domain 1, they might test positive in that test? And that is what I believe. So I believe that all people with antiphospholipid syndrome have antibodies causing the syndrome. I think that. But I just think that our tests we have at the moment can detect the vast majority of them, but there are a small number of people who can't be detected by the current tests, even though they have the antibodies, and so these are what we would now call seronegative APS. So I believe in it for that reason.

Now if other people argue a different reason, they say there are people who seronegative APS exist because there are people who look like APS, they've got all the symptoms of APS: migraine and brain fog and ((levido?)) and clots, and they don't have the tests, and so we call them Seronegative APS. I come at it from another point of view. I come at it from the point of view that I know that these antibodies cause a problem, I just don't believe we have the perfect test yet; I think there are other tests yet to be found. That's what I think. There are quite a lot of other people who think the way I think, around the world, and who are working on different tests, and that's where I think, not only does seronegative antiphospholipid syndrome exist, but that in future it will be much more widely established, maybe because there will be more tests. And I think that's how we should think, that we should be willing to be flexible about the definition, because we already know that the science has changed.

So what are we trying to do about in our laboratory at ECL? So we're interested in this domain 1, as I mentioned, and we can make it, we can make it artificially. So domain 1, you can't find it in human bodies because it's linked to all the other domains. We make it artificially in bacteria, and it's a tricky thing to do but we've now perfected the way of making it. So you might say, 'What's the point of that? Why do you want to do that?' And there are two points to it. One is, we think that if you test blood for anti-domain 1 antibodies rather than anti-beta-2 gp 1 antibodies, it might be better, it might be a way of telling people with APS apart from other people. So why is that important? Well, here's a reason why it's important. The test I showed you in the beginning, the anticardiolipin test, sometimes it's positive in healthy people. So if you took 100 healthy people who didn't have APS at all, perfectly well people, about five of them would test positive in that test. And you can see that you don't want to be diagnosing those people with antiphospholipid syndrome and putting them on Warfarin; that would be a terrible thing to do. So what I want

is a test which only picks out the Syndrome people and doesn't test positive in anybody else. There isn't a test like that yet which is perfect. Our test, the anti-domain I test, isn't going to be perfect either. I wish it was, but it isn't, I'm not going to lie to you. But our test, together with other people's tests which are being developed around the world, together all those tests, I think, will give us a better idea than we've got at the moment. It makes you better able to advise people about what's best for them. And that's why we're trying to develop that test.

So what have we found with this test? We've found that those levels are definitely higher in people with antiphospholipid syndrome than in anybody else: higher than lupus people, higher than healthy people, so that's good. And it's not just us who have done that, other people have done that: there's a group in Holland who have done it, and a group in America who have done it, and the beauty of it is, their test isn't the same as our test. We made a test which tests one way, they made a test which tests another way, and the results agree. Recently, we did a combined experiment with the American people, the same blood samples were tested in our laboratory and in their laboratory by the different tests, and the results were in very good agreement. This suggests that this anti-domain I idea might be a good one. But I have to give you a caution here: this is not the answer to everything, because we don't find, we haven't yet found, that there are lots of people with so-called seronegative APS who test positive in this test. We haven't found that yet, partly because we haven't looked yet, because we haven't got enough samples of those patients. We're hoping actually to get some from St Thomas's that we can test. So it's not going to be the answer to everything. I'm showing it to you as a principle, the idea that people are open-minded and are willing to try things in these supposedly seronegative samples to see if there are tests which would be positive. And I think, personally, and I'll be interested in Graham's views on this, that this will come to fruition. I think there will be new tests and this group of seronegative will become smaller and smaller because we'll find tests which are positive in that group.

Now the other thing is about treatments, so I said originally that I can understand very much why people would be reluctant to diagnose seronegative APS, because the implication is you have to give people this toxic, difficult drug, Warfarin. Now Warfarin has saved a lot of people from clots and strokes; I'm not going to disrespect Warfarin in this hall. A lot of people have been saved by Warfarin. Heparin and Aspirin have saved a lot of pregnancies, they are good drugs in this syndrome, but, on the other hand, they have side-effects: like bleeding, it's inconvenient to take them. The story I always tell at this point is a gentleman who I saw in my clinic, who we diagnosed antiphospholipid syndrome, and he said, 'Okay, do I have to take Warfarin?' 'Yes.' 'How long for?' 'Pretty much for ever really.' And he said, 'Well, this is very inconvenient for me because I'm a very keen hockey player, I love playing hockey. How am I going to play hockey if I'm on Warfarin? What will happen if a hockey ball hits me in the head?' Well, you don't want to be playing hockey if you're on Warfarin, essentially, and he had to stop. That was a big problem for him. He took up a gentler sport, and it may have been croquet, I can't remember, but that's what he did. And it's just an example of the way in which people have to adjust their lives. It is not trivial to have to do that. And it's lifelong, so we want something better. Doctors would like something better, patients would like something better. So where does domain I come into the situation?

So you remember that diagram I showed you of the antibodies coming in and attaching to domain I's, so our idea in my research group is to use the domain I as a drug, to put it in, block the antibodies binding to the beta-2 glycoprotein I and stop that from happening. That's what we want to do. So what are we going to do about it? So far this is what we've shown. We have shown that if we use or domain I, add it to antibodies, we can block those antibodies from binding to beta-2 glycoprotein I on a laboratory plate. And together with some colleagues in America, who have done experiments in mice, so these mice, they have a way to make them have clots, just like antiphospholipid syndrome, and when they put in our domain I, the domain I we made, the size of the clots in the mice went down dramatically; it was a treatment for the clots in the mice. Now, I don't want to make it look like I'm making outlandish and outrageous claims here. This doesn't mean that tomorrow there's going to be a drug based on domain I. No, there's a long way to go and we need to do more experiments and we need know it's safe in people, but this alone is encouraging, the fact that it can be done. And again, it's not just us, there are other people

who are looking at different ways to block these drugs. And why am I telling you this? Because I don't think that we will always use Warfarin and Heparin. I think there are going to be better things, and those better things are going to come out of research.

So coming back to where I came in, which was the idea of why is it so difficult to be put on to Warfarin for seronegative APS? Number one: because of the original definition, people are reluctant to diagnose it, and that doesn't make them bad people, it's because the definition says you can't diagnose it. That's what the definition says, if you go by the definition in the book. So it's a leap of faith to diagnose it. And the second thing is: is you do diagnosis it, there's this treatment which you don't really want to give people, but if there was another treatment, which was much more benign and had fewer side effects, then I think people would think completely differently. And for the reasons I've shown you today, I think the future will be better than what I saw on Hughes Syndrome Facebook page.

Thank you.

Chairperson (Professor Graham Hughes): Thank you very much Anisur. Doctor Rahman won't be able to stay until the end, so I'd be very grateful for any questions of interest while we're waiting. I can tell you a worse story than supporting Bristol, and that is my wife and I were married for 45 years before I discovered she was as secret Charlton Athletics' supporter!

Any questions? Yes.

Q1: I just wanted to ask you, most of us have been diagnosed using the traditional definition of anticardiolipin plus LA, lupus coagulant, and you've said that over time these definitions have changed, and in fact more knowledge has been generated after research. Do you think based on what you've said, especially with domain I, there are seronegatives who are still APS positive, and some of them are positives but still not APS? Could there be a situation where there are false positives for APS, using the traditional definition?

AR: Okay, that's a good question. So the question was: can the traditional tests give you false positives, people who test positive but they don't have the condition? So it's certainly true that people can test positive who have never had a clot or a miscarriage; that is definitely true. And one of the big conundrums in medicine is what to do with those people. So I work in lupus, and in lupus probably between 20 and 30% of people would test positive in one of those tests. Now what do I do with a person like that? Do I say, 'You're highly likely to get antiphospholipid syndrome so you should take Warfarin or Aspirin?' I have no basis to say that, because you just don't know what's going to happen to that person in the future. So I don't like to call it a false positive because some of those people may, in the end, get APS. There are definitely people who test positive in those tests who will never ever get APS, because they don't have the type of antibodies which cause that. Research is directed at finding tests which will distinguish the dangerous antibodies from the not dangerous antibodies. The best we can do now, as clinicians, is to add up the risks and advise the patient. So if I'm in that situation where a patient is positive on one of these tests, they've never had a clot, they've never had a miscarriage, I would ask somebody like Beverley, who's a haematology specialist, to help me, they'd do a screen of other clotting tests to see what exactly is going on, what is that person's risk? And obviously advise some sensible things, like not smoking, for example, things about airline flights, but in the end it's a judgement call.

Chairperson (Professor Graham Hughes): At the front.

Q2: First of all I'd like to thank you for bringing up this subject matter because it's actually something that people do get quite emotional about. My question is: what happens to people who are diagnosed, and then get moved to

different doctors and then they take that diagnosis away? What do those people do for their treatments?

Chairperson (Professor Graham Hughes): That's a very interesting question.

AR: And it's hard for me to answer because it's not something that I would normally do. If somebody came to me with a diagnosis, I wouldn't, in general, say, 'Your last doctor was wrong, they made a mistake.' Now, what I might do, is I might say, 'Well, your tests are now negative. Let's look at what the issues are here, what your risks are, what actually happened to you in the past.' So let's say, for example, it was a lady, and her problems had all been during pregnancy, she'd only had problems during pregnancy, her tests now become negative, and she's past that time in her life where pregnancy is likely to be an option. So I might say, 'Well, look, whether you had it or not at that time, those sorts of things are not likely to happen to you anymore, so does it matter whether we call you APS or not?' I might say that to a lady, but I wouldn't say, 'Your last doctor was wrong,' because I think that's unnecessarily confrontational. I think it's a very, very difficult situation for any patient if they feel that they're under two doctors who disagree with each other, and I think as doctors we should generally try to avoid that situation because it's difficult for the patient. And I go by what's called the Physician's Mother Dictum: you should treat the patient in the way you would treat your mother. And I should add that my mother never listens to me!

Q3: Talking about the same type of patient, but if you haven't had a clot but you've got very strongly positive antibodies, you've got very bad symptoms, you can't work, etc, etc, and brain-fog, would you treat that person with Warfarin? Personally I am on Aspirin but that's all.

AR: So this is a very fascinating question, what you've just said. So I'm going to take it in two parts. The first part is you have people with sky-high levels of antibodies who haven't had a clot yet. So maybe they're going to have one, are you brave enough to put them on Warfarin to prevent their first clot? Once they've had a clot, nobody's going to argue, you're going to put them on Warfarin, but why do they have to have the ((?)) It all depends how you and the patient feel, because it's easy for me to make the prescription, but I'm not living with the consequences, I'm not taking the Warfarin. So my view on people with very high levels, particularly if they're positive in more than one test, and they've got other risk factors, is probably to err on the side of prescribing it just on the basis of preventing clots, and with advice from haematologists. Now with regard to the other symptoms you described, the brain-fog and so on, I personally don't feel I have enough experience to advise. So I haven't seen enough people who have benefitted with those symptoms from Warfarin. So in that situation, which arises very rarely, I usually refer to people who have more experience, which essentially is St Thomas's.

Chairperson (Professor Graham Hughes): Thank you very much. Two more questions. The gentleman over here.

Q4: I'm a GP from the south coast and have diagnosed patients with APS. I've got a patient at the moment who is young, who has had recurrent migraine, very severe, with hemiplegic results from that and effectively a stroke, but her tests have all come up negative. My feeling is that she's probably one of your APS negative patients, but I'm a GP and putting her on to Warfarin or Heparin probably wouldn't be suitable for me to do, but I'm also in an area where they wouldn't necessarily be happy to diagnose APS with negative tests, and I'm not quite clear what to do. She wouldn't be able to come up to London because she's disabled from the stroke as well, so I'm a bit stuck about how to help her.

AR: Okay, so my view on that is firstly, if I were a GP I wouldn't make the decision myself, and you're going to need a haematologist anyway if you're going to put her on Warfarin or Heparin. And I would say to look at it from the patient's point of view. Now if what we have is somebody who has relatively mild symptoms and you're contemplating putting him on Warfarin for a long term, it's a risk benefit: there are risks of Warfarin and there are benefits. You might say the benefit of getting rid of a mild symptom is not worth it. You're not talking about that, you're talking about somebody who has had a stroke, who's quite severely disabled. In this situation, I would sit down

with the patient and I would say, 'Look, there is a treatment which might help you. There are definitely risks to this treatment, there are drawbacks to this treatment, but look at where you are the moment, what do you think about trying this treatment for, say, a three month period and monitoring you, and see if you get better?' And the patient has to take part in the decision, the patient is living with the consequences, and so if the patient says, 'Look, my quality of life is terrible, I'm always terrified I'm going to have another stroke, I want to try it Doctor,' I think I'd do it.

Chairperson (Professor Graham Hughes): We have to move on. Can we answer some of those questions at the end?

Lynn Kirwin: Hello, I'm Lynn Kirwin from the Hughes Syndrome Foundation, and in response to the difficulty of getting treatment in the southwest, I just wanted to point out to everybody that we have a wonderful new website with a list of 80 clinicians around the country who do treat APS, so do look at our website.

Chairperson (Professor Graham Hughes): Thanks very much.

Craig Givens and Yvonne Wren: A tale of two testers: with support by Roche Diagnostics


Craig Givens:

Good afternoon, my name is Craig Givens. In September 2004 I was diagnosed with cerebral antiphospholipid syndrome and I was started on warfarin soon after that. I had had a series of transient ischemic attacks, TIAs or mini-strokes, that affected my balance and rendered me dizzy most of the time. My INR target range was set at 4 to 4.5, and for the first few years my INR proved very difficult to stabilise. I was going to the anticoagulation clinic at least every two weeks, and sometimes up to three times a week, and although the clinic is not that far away from my home, each visit would take up to at least half a day so I was spending a lot of time there. I did get a lot of reading done while I was waiting!

Over the first few years I had several INR related health incidents that landed me in A&E. In 2005 I suffered a further TIA. My INR had dropped to 2.7 after a pharmacist in the clinic had reduced my warfarin dose strictly according to protocol. A word of explanation here, protocol if you don't know in this case is the official guideline for calculating the alteration to your dose of warfarin if your INR is either too high or too low. The protocol is based on the effect of the drug on clotting factors in the blood of the average person – more about that later.

I also ended up in A&E three times with severe nose bleeds, and once with a cut to my lip that I couldn't get to stop bleeding. Two of these incidents resulted in hospitalisation where my INR was discovered to be way above my target level. In 2008 I had a serious fall from a ladder resulting in massive bruising and a large haematoma in my thigh. I was lucky that a neighbour just happened to drop by and found me. My INR was later discovered to be over 7, hence the massive haematoma and the bruising that followed. I was in hospital for several days while the bleeding was brought under control, followed by weeks of physiotherapy in the haemophilia centre to clear the haematoma.

Later in 2008 I was beginning to get fed up with the amount of time that I was spending at the clinic. I also thought there must be some way for me to keep closer tabs personally on my INR and hopefully to reduce the rate of INR related incidents. I had begun to be aware of my body's responses to changes in warfarin dosing, for example my INR would fall very, very fast when my dose was reduced, but it was very slow to climb back up again after it was



increased. I discovered that many other APS patients experienced very individual reactions to changes in their warfarin dosages. I also learned that the higher the INR level the more unstable it is. The average target range of patients undergoing anticoagulation across the board is between 2 and 3. For APS patients the average target range is between 3 and 4.5.

This presents a dilemma in dosing APS patients, generally we have a higher than average target range and therefore we tend to be more unstable. As we're on long-term anticoagulation, many of us come to know the idiosyncrasies of our personal reactions. If we dosed according to protocol, that should be tempered with a knowledge both of APS particularly, and also a knowledge of the tendencies of each individual patient. Personally, I think this is best done in a direct conversation with the clinical nurse. On the other hand, if we're dosed strictly by protocol alone and instructed by email, answerphone or text, we're often in trouble. I've experienced that. I've been over diagnosed and under diagnosed by this approach because my personal reactions to the drug weren't part of that equation.

But to get back to self-testing, I had seen some information about this, the publications of Anticoagulation Europe, in leaflets from Roche, and it had been spoken about at Hughes patients' days such as here today. This I thought is definitely worth looking into, so I talked to my GP, to the haematologist under whose care I was, and also to the nurses in charge at my anticoagulation clinic. The responses I got were amazingly different. My GP was very supportive and immediately offered to buy the machine for me, but then he found out that the Primary Care Trust or PCT would not allow this to happen. However, he did reassure me that he would prescribe the strips and he would give me his full support as long as my haematologist was in agreement.

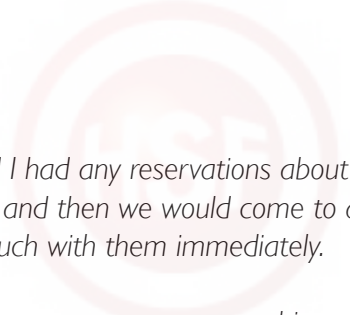
My haematologist gave me an information pack with a DVD about the CoaguChek XS machine and unofficially encouraged me. In a letter I was told, 'With regards to dosing, a man with your intelligence should be able to manage it. You have to remember that the doctors and anticoagulation staff learn on their feet and do not have the understanding when they start as you do first-hand about warfarin. So I think you should do very well'. However, when I spoke with the nurses in charge of the clinic I received a very different response, they absolutely did not, would not, support self-monitoring, and if I went down that road they would have nothing further to do with me.

It took over a month but finally I was able to have a face-to-face in-depth conversation with the consultant in charge of that clinic, who eventually confided to me that neither he nor the PCT could or would endorse self-testing officially, it was a matter of policy. But he did think that I should give it a go, and he told me if I had any problems I should get back in touch with him personally and he would be glad to advise me. So, confusing or what?

In conversation with other APS patients I came across some who were self-testing, some self-dosing as well, many of these on the sly as it turned out. This seemed very risky to me and not a gamble I was prepared to take. However, some self-testers were with PCTs where it was supported, as you'll hear from Yvonne later. As it so happened the neighbouring PCT to mine did support self-testing, so after investigating I registered with them, which involved signing a contractual agreement covering self-testing. I then bought a machine and started self-monitoring. I never did de-register with my original clinic as the rest of my APS healthcare was there and I valued those connections highly, they had truly been a lifeline for me. So for a while I attended both clinics.

From the start I have kept a close record of my self-testing results with dates, INR levels, dosages, venous sample comparisons, and any other relevant observations that I have made. I've been able to form a clearer picture of factors that affect my INR such as diet, alcohol consumption, and of course interactions with other medications. Surprisingly, I found that long-haul flights have less effect on my INR than I would have thought, but that stress like road rage, standing in long queues in Sainsbury's, can send my INR through the roof.

Over time the attitude at my original clinic has changed. Each time I go I take a print-out of my computer chart for them to see. It was obvious how much more consistent my INR levels were becoming. I observed increased interests



from the nurses as they watched my progress. If a change of dosage was needed and I had any reservations about the proposed alterations, the nurse would listen, take my proposals into consideration, and then we would come to a consensus. I also assured them that if I had any difficulty whatsoever I would get in touch with them immediately.

Each time I start a new set of strips I go to the clinic once a week for three weeks to cross-compare my machine reading with the venous sample. My visits to the anticoagulation clinic have reduced to once every six to eight weeks, or even less. I generally test once or twice a week, but my aim is to reduce that to once every two weeks. Since I've started self-testing I've been to A&E only once, and I've not required hospitalisation at all. I've been able to keep tabs on my INR, keep it more stable, and take precautions if I surge or if I drop. I can travel with much more peace of mind with my kit, which is my CoaguChek machine, a supply of clexane for emergencies, and a letter from my GP requesting that my INR be tested if need be.

The policy in my PCT is in transition, they are at present putting together a contract or agreement to enable patients to self-test and be supported by them, so things have changed and they are changing. I do realise that the situation across the country is far from uniform and there is a dark cloud looming on the horizon now that the Primary Care Trusts are being replaced with something called Clinical Commissioning Groups or CCGs. With the current cuts and reorganisations, patients who had been self-testing and who are receiving test strips on prescription, may well find that this is no longer available. I've been told that such incidents have already been reported. We may have to pursue this battle for self-testing all over again.

Financially this would appear to me to be very short-sighted as the benefits of self-testing are beginning to be recognised here as well as in other countries. In Germany for example, they have found that self-management is less expensive for their healthcare system. As far back as 2007 they estimated that the annual cost of healthcare for self-managers was approximately 686€ compared to just over 1,000€ for conventionally controlled patients. This represents a savings of roughly 35% and it's due to the reduction of hospitalisation, surgery and rehabilitation in cases of bleeding and clotting complications.

When I began self-testing my prime motivation was to reduce the time I spent at the hospital, but surprisingly a greater benefit is that I feel such a reduction in the uncertainty and the fear of what my INR is doing, much less panic about INR fluctuations, which can be adjusted, they can be managed. I'm so much more confident in my ability to manage my health, and I now have the back-up and support from my doctors as well as my other health carers. I believe that there's so much to be gained from self-testing that I do urge any of you who are able and interested to enquire about it, from many and various sources gather information and support from wherever you can, and try to put together what would work best for you and for your situation.

As for the uncertainties that lie ahead, I would urge everyone to keep abreast of the changes afoot in the National Health, push for self-testing, and let's meet back here next year to see where we are, hopefully having made some progress. Thank you.

Chairperson (Professor Graham Hughes): We'll go straight on, thank you very much, and we'll keep all the questions to the end. Yvonne.

Yvonne Wren: Thank you. Hello, my name is Yvonne Wren. Can I just say that we have two representatives from Roche Diagnostics here, Oliver Lawrence and Rebecca Oakley, who I know are happy to answer any technical questions about the CoaguChek XS machine at the end of the session today. Just to let you know, I retired from the NHS in 2008 after 37 years working as a physiotherapist, so I had had a little bit of medical background which was helpful for me.

My journey too and experience of self-management is quite different to Craig's, and highlights the discrepancies that can occur with patients on warfarin who may wish to self-test and/or self-manage. I was diagnosed eight years ago

with primary APS in April 2005, after 18 months of investigations, years of symptoms, and several undiagnosed TIAs, transient ischemic attacks or mini-strokes. I've been self-managing for seven years, since April 2006, so that's self-monitoring with a CoaguChek XS machine and self-medicating by adjusting my warfarin doses appropriately.

When I was first diagnosed I was attending the anticoagulation clinic once a week at my local hospital in South London. This went on for a year. The therapeutic range for my INR is quite high, it's 4 to 5, and I'm not sure if everybody is aware of the term INR, but just to remind people it stands for International Normalised Ratio, and it's a measurement of how quickly it takes your blood to clot.

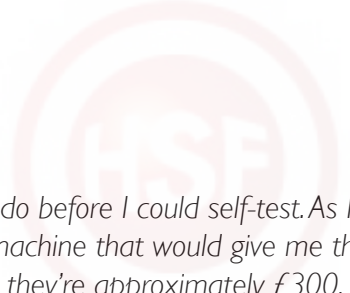
With the combination of APS and a high INR it's really hard to keep it in range. The visits to the anticoagulation clinic were time consuming, restricting, and additionally expensive to the NHS as they were not only paying for my attendance at the anticoag clinic, but also my salary for the afternoon off work as clinic appointments and travel were never less than three hours at a time.

I became aware of the possibility of self-managing through the Hughes Syndrome Foundation, and I was informed that there were several things I had to do though before it was possible. Firstly, I had to check with the anticoagulation clinic nurse specialists that they would agree to support me. My anticoagulation nurses have been brilliant, they drew up a contract between me and the hospital which we both signed, to say that I would contact them if my INR was much outside the therapeutic range, either above or below on any occasion. They take venous samples three times a year – that's blood taken from the vein – to validate the calibration of my CoaguChek XS machine. In other words, to make sure the machine is giving the correct readings. Interestingly, although I am lupus anticoagulant positive, the venous and machine readings never really varied for me more than 0.2, except last month, two days before I was due to fly out to New York for a 16 east coast of America road trip, and my INR reading from the CoaguChek XS machine was 0.7 higher than the venous sample.

I rang Roche Diagnostics to find out if I could have my machine checked, and they said yes I could but it would have to be sent to them and would take about three weeks. I explained I was about to leave the country, and they suggested I asked the haematology staff at the hospital if there had been any change in the procedures in the laboratory or the reagents or the test strips they were using, as this was a common cause of variation. My lovely nurse specialists at the hospital asked me to come in the next day and get my INR checked on the CoaguChek machine that they now use in the clinic, and I did that, and there was only a 0.3 variation, but that I would have to monitor my INR very carefully when I was away and be aware if there were any neurological symptoms, to check it on those occasions especially. She also offered for me to come in twice a week for her to check my INR if I needed to send my machine back to Roche for testing on my return.

The nurses have also taught me how to self-inject with heparin, and they've supported me through surgery twice. I try to keep my INR as low as possible within the therapeutic range, but also to keep symptom free. If it goes too low and I experience neurological symptoms, I have to self-inject, which I can now do with confidence. The nurses have also attended a course of APS and read up about it, and encourage me to ring them for anticoagulation advice whenever I need to. This is an ideal set up and I know I'm very lucky.

Secondly, on the route to self-management I had to check with my GP that they would be prepared to fund the test strips for the machine on prescription. My GP has said the test strips will be available on prescription for the foreseeable future. But this has been a problem in some areas of the country, and you can never be certain with funding if things will continue, particularly – as Craig mentioned – the Clinical Commissioning Groups are now replacing the Primary Care Trusts and GPs now have more responsibility over their own budgets. However, my GP's also informed me that she and three other GPs from the same practice, have recently attended the GP course on APS at the London Lupus Centre based at the private London Bridge Hospital, and found it extremely informative, so the GPs have been very helpful as well.



Thirdly, I had to find the money to buy the machine, that was the other thing I had to do before I could self-test. As I wanted to travel more, I considered borrowing the money to buy the CoaguChek XS machine that would give me the freedom and confidence to do more travelling. At that time it cost £400, I now believe they're approximately £300. But as luck would have it, I won a lump sum at bingo and was able to buy it outright! It was my priority.

I've heard several horror stories from anticoagulation clinics about them washing their hands of people who want to self-test, or of GPs refusing to prescribe the test strips, but organisations such as ACE, Anticoagulation Europe, and ACSMA, Anticoagulation Self-Management Alliance, are trying to put pressure on MPs and health professionals to find ways to change this. I've been able to travel widely with my CoaguChek XS machine, I've been to Iceland, France, Spain, Las Vegas, several other American States including Hawaii, where I was able to avert a TIA by monitoring my INR when I started to have neurological symptoms, which may have been caused by the exhausting long distance travel, or certainly contributory, and I was able to take quick action to stabilise my INR.

And I've just come back from an east coast USA road trip five days ago. My INR was completely in range for the two weeks I was away, until the penultimate day when I tested it and it was 3.9, just below my therapeutic range. Just prior to that, and the reason I tested it was because I'd been getting some strange numbness and tingling in my face and my left leg and some other symptoms. I checked my INR in the morning of return travel, which included a one hour flight followed immediately by a seven hour flight, and the INR had dropped to 3.6. At that stage with the pending flights and the declining INR, I decided that I needed to inject myself with heparin immediately before the flight, and also I increased my warfarin dose by 0.5 milligrams that night.

I checked my INR on return to the UK and it continued to drop, went down to 3.1, which was very low for me, so I continued with the heparin injections until I was nearer the therapeutic range, and I increased my warfarin again by another 0.5. I monitored the INR daily at first, and have contacted my nurse specialist at the anticoagulation clinic, as agreed in my contract with them, to inform them of what I did while I was away and since I got home, and to seek advice as necessary. I also followed the travel advice which I went on the new Hughes Syndrome Foundation website, just to make sure I was doing my injection at the right time before flight, and there is a fantastic self-help travel section on the new website.

I appreciate how lucky I am that all these factors have come together, so between the anticoagulation nurse specialists, the GPs, being able to fund my machine, and the hospital consultants in haematology at Guy's and St Thomas', they've all been supportive, and that really this should be the blueprint for everyone and one that we should all aspire to ideally. If you're not having any luck with your health professionals, try to access information on the Hughes Syndrome Foundation and the Anticoagulation Europe websites, and you could sign up to the Health Unlocked website and join the Hughes Syndrome Forum, as they all have useful information that may help to achieve assistance with self-management on warfarin.

For those of you who wish to self-manage or self-monitor, I wish you good luck. It has been the most rewarding and liberating experience for me thanks to the support that I have received.

Thank you.



Sander Otter: The Dutch APS Approach

Sander Otter: Hope everyone can understand me. I try to do my presentation in English because I consider my English is probably better than your Dutch!

So, I was diagnosed in 2008 with the antiphospholipid syndrome. The doctor who diagnosed me gave me a little note with the name of the disease, in fact wrongly spelt and she told me for further references to take a look on the Internet. So I did and I couldn't find a thing, except for a couple of sad stories about pregnancy and a lot of times the name of Graham Hughes, that both I wasn't looking for. So, persistently popping up the name of Graham Hughes, I decided to click advance and at that moment I landed on the pages of Hughes Support Foundation and everything went clear for me. I thought there must be a better way of organising this in Holland seeing the number of patients on the English website and I thought I would probably not be the only one in Holland. I started looking for someone who could help me and I did find the NVLE.

Ok, I did find the NVLE. It's a Dutch patients' organisation for all kinds of autoimmune diseases such as lupus, scleroderma, MCTD and since 2010, also antiphospholipid. Together we are strong and we have a lot of things to be offering all our patients and of course also the antiphospholipid patients. We do have a medical advice board with twenty-seven specialised doctors and not just pain doctors but all top of the bill and all interested in the antiphospholipid syndrome. We answer a lot of questions from patients. We have a special APS group at present set all our activities and we've got an annual meeting especially for the antiphospholipid patients. The is the first meeting and we have a gynaecologist talking about the pregnancy-related problems but we decided we could not let her have each the same talk that nowadays she is just at present working by and is willing to answer questions. For doctors, but also for patients, we are available on the social web just because of the short lines if you have a question or if you're just newly diagnosed with antiphospholipid syndrome, we can be reached easily on the social web.

Another thing we do, is the NVLE connect. We are creating a system where doctors work together with medical health professionals to give patients their correct treatment. We are creating a system that is connecting everyone together.

Another thing, is the NVLE fund and we can access money to research etc. In this particular case, a woman who was working with a big insurance company who gave for charity each year a donation. This woman collected 25,000€ for a special research which is done by Daniela Cohen who is doing a lovely job on our commission and on the research at antiphospholipid and pregnancy.

Of course we do a lot about education. We made several short movies, it's a pity that the movies are not in English language, otherwise I could have chosen, just like the professor, to show one of the movies. Movies are meant to show the life of the patient as it is for normal life, later on I try to show a movie somewhere.

We have a great looking website and of course we provide schools and universities a lot of information to our topics. Of course we do have a good looking quarterly magazine and when we started in the antiphospholipid group we made a first special number on the subject, with introducing all our doctors and everything we knew about antiphospholipid syndrome at the time.

And then there is one last final message which is very important. Whatever you do, you got to keep living. That will conclude my speech. Thank you very much. Thank you.

Chairperson (Professor Graham Hughes): *Well, thank you very much. Well, last year we had a lot of people asking about insurance and the problems of travel and getting insurance if you have APS and it's great to welcome Ed Froggatt and Edward Beaber now to tell us about the pluses and minuses of getting insurance.*



Ed Froggatt and Edward Beaber Financial Planning and Hughes Syndrome: Making sense of insurance

Ed Froggatt: *Hello and good afternoon. My name is Ed Froggatt and with my colleague Ed Beaber we'll try and make a little sense out of financial planning and Hughes Syndrome, specifically focusing on making sense of insurance. We'd like to think that two 'Eds' are better than one, but we'll leave you to decide that. Just a quick gauge before I tell you a little bit about myself.*

I just wonder without being too intrusive how many people in the room actually have life insurance or a form of health insurance? And how many have tried to get insurance or been declined or thwarted in your attempt to get insurance? Actually, sorry, not specifically travel insurance, actually health insurance or life insurance? Okay, thank you very much. How many people in the room actually feel they need life insurance? Okay, thank you.

Just a little background on me and my association with the Hughes Syndrome Foundation. I've been involved in banking and financial planning for a shade over ten years. I have experience across all areas of financial planning and after some significant changes in our industry, I recognised that working in a banking environment would restrict the range of solutions available for my clients, so I elected to become wholly independent and joined NLP Financial Management about six months or so ago. I actually became involved with the Hughes Syndrome Foundation by coincidence. I happened to meet a member who like many, was unable to get any type of health or life insurance. He was simply trying to secure a future for his family in a 'worst case scenario' and was hugely frustrated in the industry's lack of knowledge and ironically, lack of appetite to provide any form of protection or insurance. Having gone through an arduous process with a number of insurers, not only did I manage to obtain insurance where many others had failed, but I'd started to understand more about the plight that probably many of you here face today. This led to an introduction to Kate Hindell who I'm sure a lot of you know here today, who had similar experiences when faced with obtaining insurance. It was with my new-found knowledge around Hughes Syndrome and more importantly how insurers assess risk, managed to gain or secure insurance again, where many others had failed. I guess it was at this point, that what I started to understand was that there are two cases aren't the same and whilst there isn't actually a secret formula as such, there is a way to go about getting insurance that does provide hope. Before I go into any more detail on this I would like to introduce you to another slightly older 'Ed' who would like to tell you a little bit more about NLP Financial Management and our core business; so I'll hand you over to Ed. Good afternoon ladies and gentlemen. This is definitely a slightly older Ed. I've been in corporate and personal finance for over forty years, I trained as an accountant, moved into the insolvency profession and then into industry where we helped build a great fashion group which was sold. Subsequently set up a management consultancy firm, and then added financial services which soon became its focus. At the heart of the business it was always, how can I help people achieve their financial objectives and whether it be the purchase of their home, expansion of their business or providing for the family or indeed, planning for retirement. And after selling my practice I moved back into the good old corporate world and spent a couple of years helping various companies achieve their objectives; before I joined NLP Financial Management as its business development consultant.

Well actually, what's the connection? Why am I here with Ed today? Well, it's not to hold his hand. He doesn't need it. He's an experienced financial advisor with a sound track record. But actually, one of the main reasons was, that when he spoke to me about Hughes Syndrome and how it affects people, I realised that I had something in common, because one of the medications he advised me of, was Warfarin and I recalled how now my late mother-in-law battled with the side-effects of the drug and its unpredictability. She in fact had quadruple bypass surgery and then had blood clots, bleeding, until finally she succumbed to a massive stroke at the age of sixty-nine. Its unpredictability was frightening but no doubt as you know there have been significant changes since the '90s.

One of the other topics that we'll be addressing today, is that on retirement planning. Again, once again through a

very distressing personal experience, I will explain the importance of seeking experienced financial advice, when one is considering taking benefits from a pension arrangement.


Ed also wanted me here today to provide you with an overview of our company, which is NLP Financial Management and in particular, what lays at its heart, what its main focus is. We are, a boutique firm of independent financial advisors, totally independent. It was set up in 2002 by two chartered accountants, as in fact the financial services division of Nyman Libson Paul whose history goes back over eighty years. And we assist clients in financial planning through different stages of their lives. We offer a personal tailored service to each of their needs and we are fee-based and have been so since inception. We are not just there to sell product. We provide a service and we offer professionalism and complete transparency of service.

We also in our group, we have advisors who are specialists in the provision of financial protection solutions, Ed being one. We also offer a great offering of tax-efficient investments. We currently have over three hundred million of client monies under management, of which one hundred and seventy million is under our discretionary management service. Ed, over to you.

Ed Beaber: I'd like to make this slide just a tiny bit more interactive if possible, so we did put some leaflets on your seats before the event, so if you are able to open them up – it's not the end of the world if you can't; there's a small card on that with a few questions just really for thought more than anything else. I'm sure a lot of you based on earlier comments are here to understand more about why you can't get life insurance and I probably guess it's across insurance generally.

The first point on the slide is underwriting difficulties. We know many applications are completed on computers. When certain words or medical conditions are mentioned, a decision can be automatically made without consideration. Effectively it's a 'computer says no' scenario. Quite often for complex, relatively unknown ailments, data can be input incorrectly, resulting in the same outcome, so data input error. I've added on the slide 'inclusive of previous medical history'. Again, the same scenario, where a decision can be thrown out on the basis of a previous rating, so enhance terms or decline; in both cases, the key point is there is very little human consideration on application. And non-disclosure finally, where there is an automatic decline from any insurer on the basis of non-disclosure. So not mentioning something that you either do or don't believe to be relevant to the application. Probably one of the most important parts of this presentation is dealing with an experienced advisor. It is so important to approach the right company and the right individual within that company when applying for insurance. Each insurance will often have a quota on medical ailments. One company may simply not be prepared to offer terms where another will. It's safe to say that no two insurers are the same. Risk is ultimately seen differently by different companies and often, inexperienced advisors simply won't know that. Again, a key part of the slide is having no relationship with an underwriter or an insurance process, so technically, what we call a blind submission occurs, effectively where an application is submitted without prior consideration. Where I can add value is we have a good relationship with main-stream insurance underwriters. We are in a position to approach senior underwriters on a pre-submission basis, prior to a full application form being completed. We can obtain an indication if you like, of terms being offered and whilst we can't always promise success, we can at the very least manage your expectations. Ed is just going to talk to you a little bit now about how else this can affect your financial planning.

How else can - what other areas can Hughes Syndrome possibly affect your financial planning? Well, let's look at retirement planning both pre- and post-retirement. Now our objective during our working lives is to build up as much as possible to provide for our years in retirement. Typically, this is in a pension arrangement where this is provided by one's employer or a personal pension it doesn't matter, because saving through a pension is still one of the most tax-efficient means of building up capital as there are significant tax advantages. For example, tax relief up to certain levels of contributions, currently it's £50,000 and the fund grows almost entirely free of tax. Now when you reach your chosen retirement age which currently the minimum age is fifty-five, you actually have choices. The benefits from



your pension pot can be taken in a number of ways, but the most common practice today is to take the maximum tax-free cash sum which is twenty-five percent of the pot and the balance buys what is known as an annuity. Now what is an annuity? It is a payment that the pension provider pays the member for as long as he or she lives. Now people with any illness and particularly life-threatening illnesses, which could potentially shorten their lives should seek financial advice before accepting the annuity the pension company offers. A frank, open discussion about one's condition can radically improve the level of the annuity one can receive. Indeed, there may even be the case, as in the case of my late father-in-law, who should not have taken his annuity at all, but leave his pension fund intact and then it would have passed onto his widow on his death, to provide her with a pension for the rest of her life. Instead, unfortunately, it died with him only six months into retirement and the only people to gain was the pension company.

The next aspect we look at for all of our clients is inheritance tax planning and the use of life assurance plans in dealing with how to mitigate IHT (inheritance tax) NLP Financial Management has a vast amount of knowledge in this very complex area and perhaps we should even consider that inheritance tax is a voluntary tax. If one's affairs are properly arranged and use is made of the various reliefs, gifts and trusts, then the effect of inheritance tax can be considerably reduced; leaving your hard-earned capital which has already suffered tax in most cases, intact for the next generation or your desired beneficiary. IHT is very, very complex and it deserves investing time to ensure that Her Majesty's charities don't benefit too much from you.

NLP also looks at the preservation of wealth and this is the core business of our company. We offer both, as we'll advise, both a discretionary and an advisory investment service. Our clients have typically built up their funds and they want to ensure that these are not subject to undue risk or volatility, which is typical of what's happening in the markets today. We are recognised by our peers and clients as a 'safe pair of hands' and that I believe is in your brochure there. We also offer a cash management service and this was provided to ensure that clients obtain the best rates of interest on their cash. Rates are checked weekly and clients' funds are switched only if appropriate, in line with our discretionary licence.

Finally, ladies and gentlemen, NLP is determined and committed to help the Hughes Syndrome Foundation and we will be donating twenty percent of all initial fees generated back to the foundation for future research and support. Obviously I understand that questions are going to be at the end of this session, but if there's anything that you wish to speak to us about, please do so and also complete your cards on your chair in the pack afterwards. And obviously please also visit our website because there is a direct hot-link between us and the Foundation. Thank you indeed ladies and gentlemen.



OPEN FORUM

Participants:

Panel:

Professor Graham Hughes
Sander Otter
Craig Givens
Yvonne Wren
Ed Froggatt
Edward Beaber
Professor Beverley Hunt
Kate
Male speaker

Questioners:

Will Stammers
John Allison
Gordon Hopkins
Unidentified speakers

Chairperson (Professor Graham Hughes): *Well, thank you very much, I'm sure that's generated a lot of questions. We now come to the busy question and answer section, and I'd like all the speakers to come forward on stage. I'm sorry, it's a bit like a stage show, and if we could borrow one of the roving microphones for the speakers' answers and the other one for the people in the audience and perhaps the lights up, if they will. Thank you. Any questions and answers? Let's start. The gentleman in the front?*

QI: *Thank you. My name's Will Stammers. It's my son actually who's the Hughes Syndrome sufferer, and we bought for him one of the INR checking machines from Roche, and very promptly dealt with in a most efficient manner, but the results that he was getting from that differed quite widely from the results that he was getting at the haematology clinic. We contacted Roche over this and they immediately said to send it back, we had their PR department on worrying about whether any of the results had resulted in anything that shouldn't have happened and we said no and they sent us our money back. But, we still hear so much about self testing and this particular machine, I was wondering whether we should go back to buying one for my son?*

Chairperson (Professor Graham Hughes): *Yes, well one of the two Roche colleagues?*

Male speaker: *I think what you quite rightly mentioned was it's a two pronged answer really, the first part is that everybody purchasing devices is made aware from the beginning that there sometimes is a prolongation of the INR result, so where you do experience, occasionally when you go back into your hospital site and you do take blood out of the arm and compare it to our device, there will occasionally be discrepancies. It's usually found in a very small proportion of patients and Professor Hughes is very versed I'm sure in this area. So we have to be careful about our recommendations, and what we don't want to be seen doing is openly recommending without healthcare professional support.*

So the first part of your answer is it's good that you did have, obviously, support from your healthcare professional, you did notice that difference between results. The second part, and again, there's clinical input here from members of the team, there are clear benefits, as Yvonne and Craig have mentioned, and I suppose it's again open to a

discussion between you and the healthcare professionals should it be something you look at again, bearing in mind the knowledge that there may be a deviation between results.

Chairperson (Professor Graham Hughes): *Is there a big take up in Holland for the machine?*

Sander Otter: *Yes, we use the machine in Holland and they are also from Roche, but in my particular case the machine is not working, due to a factor ((0:03:18?)) and perhaps by more people, but normally when you are on the coagulation you can get a machine for free and then the insurance pays for the strips.*

Chairperson (Professor Graham Hughes): *Thank you. While we're waiting for – can I just ask a question about insurance? Travel insurance has been a problem for a lot of our patients, is that something you can talk to?*

Ed Froggatt: *Yes, we can absolutely we can look at travel insurance. We're going to be around probably for refreshments afterwards so we're more than happy to pick up on individual cases. It's quite a specialist area but we can certainly point you in the right direction at the very least.*

Chairperson (Professor Graham Hughes): *Thank you. A question here and then at the back.*

Q2: *It's a comment rather than a question to this gentleman. I've been self testing for longer than I can remember now, I had the original Roche before the Excess, I can't remember what it was called, the big one.*

Male speaker: *Quite a bulky thing, yes.*

Q2: *A bulky thing, yeah. And then went on to the Excess. I've always had a variation from my machine to a venous draw, it's always a relatively consistent variation. I think a lot of self testing is about confidence and getting a history and knowing yourself. I can concur exactly with Craig and Yvonne, I travel globally for my business, I couldn't exist without the machine, I have primary APS and I've had it for 14 years. This young gentleman diagnosed me some time ago. I'd go back to it and stick with it, I refuse to go to clinics when the doctor wanted to reduce my warfarin level because my INR was over two. I asked him what condition he was treating me for and he couldn't answer the question. I asked him to sign a letter to accept responsibility for my life if I had a stroke and he didn't know what to say. And that was the last time I walked into a warfarin clinic. And I've self tested since then. It's a joke in a lot of cases, they don't ask you about exercise, diet, all sorts of things which affect. Self testing for me is the only way to do it, sorry.*

Chairperson (Professor Graham Hughes): *It's my religion, I agree with you. And back behind here?*

Q3: *Hi, this is another comment about the self testing. I saw the leaflet about the self testing machine in my doctor's surgery and it said on the back that strips could be prescribed. I bought the machine, my GP surgery would not fund the testing strips at all. I had to then ask for the group of GPs that they belonged to if they would fund it and they wouldn't. And after paying for the strips myself for 18 months I then went to my local MP's surgery and pleaded the case, took all my medical history, backed up the fact I'd had TIA, stroke, all the rest of it, made the case. He took the case up for me to the PCT and the PCT then have paid for the strips.*

Chairperson (Professor Graham Hughes): *Well done.*

Q3: *But they only provide me with two packs of 24, but those come direct from my anticoagulation specialist nurse on the assumption that I go regularly to see her and I'm able to text or phone her and change the warfarin levels. And it's worked.*

Chairperson (Professor Graham Hughes): *Craig and Yvonne, do you want to say anything about that?*

Craig Givens: *You said they only supply the two, the double 24 pack. Is that annually or-?*

Q3: *Annually.*

Craig Givens: *Annually?*

Q3: *((inaudible))*

Craig Givens: *Wow!*

Q3: *It's certainly better than nothing and I think it goes to show that if you make the effort to go and push for what you need and what you want it's worth doing. The Anticoagulation Europe website have a pack to advise you how to go about trying to get your test strips on prescription. So it's worth trying to get the information from anywhere you can and to push for it.*

Chairperson (Professor Graham Hughes): *Any other questions? Yes, the gentleman here and two at the back.*

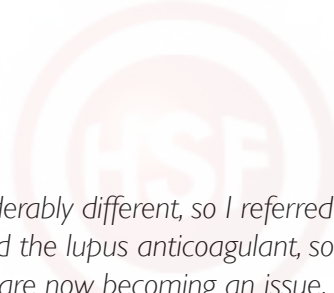
Q4: *This is about self testing again, I have been self testing a little over a year now and it's definitely great to have the machine by yourself if you can test yourself, but I have a feeling that the testing works well when your INR is actually well in control, so between two to four. So a lot of people will have a range between two and three or three to four and mine is between three and four. But when you really need to test yourself is when you doubt yourself that your INR is either below par or above level, and in those situations I have a feeling that actually the self testing machine is quite limited. So it's a bit like a fair weather play, it plays well when everything is good and it sort of kind of doesn't give you the right accuracy when you really need to know whether you are way above or way below. So my question is basically are there like a list of situations or conditions or scenarios where self testing cannot be totally relied upon?*

Male speaker: *So again, I'll answer that in two ways. Speaking around the accuracy of the device, we have an accuracy between 0.8 and eight, so it will give you that result and it has been qualified as being accurate. What you maybe refer to is consistencies, or inconsistencies between patients which may be related to your condition almost entirely. So your results may, you feel, stray slightly as they go higher in terms of its reading. That may be entirely focused on you, other patients may experience, I'm sure Yvonne may have her own depiction of how the results look the higher the INR. It's certainly nothing we experience in ordinary cases but where the lupus anticoagulant is present that's something you may experience. So I'm sure again there can be something –*

Chairperson (Professor Graham Hughes): *I thought they'd changed that. They used to say didn't they that if the lupus anticoagulant is present it messes up the test. Rubbish. Can you get rid of that on your piece of paper?*

Yvonne Wren: *Just to answer what you were saying, if I experience symptoms like my memory's poor, I feel very muddle headed as soon as I get up in the morning, if I've got some facial numbness or much more tinnitus than usual I will test to see if my INR has dropped, and if it drops significantly then I will have to inject myself as well. Also, just to make sure because I am self medicating, self dosing, I can adjust very finely, because any big changes which I found initially at the anticoagulation clinic make a dramatic change, whereas I can adjust 0.5 milligrams and monitor and get my INR back in range very quickly like that. So it is worth monitoring.*

Chairperson (Professor Graham Hughes): *There's two questions at the back and a lady at the right hand side afterwards.*



Q5: *Hi. I was using the CoaguChek machine having parallel readings that were considerably different, so I referred back to the haematologist and was told that I couldn't use the machine because I had the lupus anticoagulant, so I'm back on venous testing and obviously have been for years and obviously my veins are now becoming an issue. But from what you're actually saying is that if you don't think it is the lupus anticoagulant then what is causing the difference in the readings, is my first question. The second question, if it is the lupus anticoagulant is there any likelihood that the machine can be modified or the strips so that I can go back on it basically?*

Male speaker: *Okay, so the first one was related to more around the reliability and accuracy of it, and I know Professor Hughes probably feels like strangling me now because we don't change our position on how we approach patients with antiphospholipid, whether they have the lupus antibody. We have some evidence from the past and enough reason to suggest that there may be an extension and differences between results which you say you've experienced. We're also clear that patients are using them but they need to be supported by their healthcare professional, what we don't want really at all are patients taking it upon themselves to test outside the comfort of a relationship with their healthcare professionals, it's not something endorsed in any area really. So I would say that if you do have any concerns please re-address them to your healthcare professional. If you want to catch up with us afterwards we can also exchange details and maybe we can provide certain amounts of information.*

Yvonne Wren: *Can I just say something on that? I think this lady said it, you have to bite the bullet and really be brave, and if you go to the clinic and self test there are often discrepancies often related to the reagents they use, the technique they use, so you will get variations and it's very confusing. When I first started, very quickly I said I can't be doing with this, because they're telling me one thing and I'm reading another, am I going to self test or am I not going to self test? And I think you obviously do have to have the support of your health professionals to self test.*

Q5: *((inaudible))*

Yvonne Wren: *Again, I mean venous samples and the CoaguChek often vary.*

Chairperson (Professor Graham Hughes): *We're not sure of the reasons this happens, but in the old days they thought it was lupus anticoagulant. That is not the case and there's very good work, a lot of it from Holland actually showing that that's not the case. So I think don't be put off by that. This gentleman?*

Craig Givens: *Sorry, can I just ask the lady too, you said significant variations?*

Q5: *((inaudible))*

Chairperson (Professor Graham Hughes): *I can't hear you?*

Q5: *((inaudible))*

Craig Givens: *Because I didn't know you were talking about that sort of error, but the sort of margin of error, I have found very different and when I change a batch of strips it can go from 0.1 to 0.4, the differential between the venous sample and the strip sample, but within that range, to me it seems every batch of strips is fairly consistent and that was the rollercoaster that I wasn't prepared to do because it was like, oh my God, something must be horribly wrong. But even when the margin is larger it stays consistent to me.*

Chairperson (Professor Graham Hughes): *Yes, thank you. The gentleman here?*

Q6: Hello. I've got the Excess machine and I get two packets of strips a year. You have to buy the prick things, the lancets. For me it's given me the confidence of knowing that I'm safe, it saves me a tremendous amount of time because it's a morning by the time I've been to the clinic and back, but what I've found is over the years I know when my INR is wrong, for me with an INR of three I can hardly speak and my balance, my fatigue, the brain fog and everything else, so my INR today is probably about 4.5, 4.7, but I've found the Excess machine is great because you can take it on holiday, if you're away on business you can take it and I would suggest everyone should have the machine. I know it's fairly expensive and there seems to be an issue with getting the strips but I get just two boxes a year, but I can go to clinic as I need to as well. So the nice thing that I have is my GP now has the professional CoaguChek machine and I do my finger prick, I ring the nurse with my result, she puts it into the machine, into her computer, and she then comes back to me with my ongoing dose and it hardly ever changes.

Chairperson (Professor Graham Hughes): Thank you. Can I say that for the GPs, if you have your own GP who you'd like to nudge in our direction, we hold a GP meeting on antiphospholipid syndrome and lupus twice a year on a Saturday morning, January and I think October, the next couple of months, and we have room for 200 GPs and it's always full, so spread the word.

Q6: Spread the word, yes. I have one other question if I may on insurance.

Chairperson (Professor Graham Hughes): A quick one.

Q6: And that is if you've taken out life insurance say 20 years ago when you took your mortgage on and you now develop, since you took out the insurance, Hughes Syndrome and you die from it would that policy then pay out? Because the policy was taken before you had it.

Edward Beaber: Yes.

Q6: I can sleep better tonight then.

Edward Beaber: You can sleep better.

Ed Froggatt: Just to add one point on that, most definitely don't cancel it.

Sander Otter: One thing about insurance, I have a lucky combination that my health insurer is the same one who insures my travel, so either way I'm covered.

Chairperson (Professor Graham Hughes): Many questions, so let's move on fast. Over here?

Q7: I love my machine as well, but I just want to ask, this morning on the BBC it mentioned dementia again and the problem in the future with all the patients who are going to have dementia. But there's nothing ever mentioned about Hughes Syndrome and what's causing these people to have a problem. I know I thought I was going to get dementia in the beginning, there must be a lot of other people like that too. So I just wondered, could there be more done in this country to explain to the doctors that they should be looking out for this problem?

Chairperson (Professor Graham Hughes): Yes, definitely. It's really a passion of mine, I mean I would bet 90% of patients come to me secretly worrying that they've got early Alzheimer's Disease because they've forgotten the school run or they've forgotten words and so on. And what's so exciting is it's totally reversible, totally preventable if you catch it. And my first slides showing some Alzheimer's are not Alzheimer's, in fact they're micro sluggish circulation. And the brain is a pretty stupid thing, if it doesn't get enough oxygen you either get balance problems, headaches, atypical multiple sclerosis, you name it, we've even had people with autonomic dysfunction who faint all the time, these are all

things that the brain is not telling the body about and this should get out, especially to the world of neurology, they're the people who should be coming twice a year to our meetings at London Bridge. I sound a bit like a preacher.

Sander Otter: One of the big problems in Holland also, everyone knows the disease and not knowing what exactly is happening, so we are as a NVLE foundation particularly active in pointing out the right doctors.

Chairperson (Professor Graham Hughes): Good, thank you. Over here, yes?

Q8: Has the foundation heard anything back from the DVLA about our driving?

Chairperson (Professor Graham Hughes): Is Kate at the back?

Yvonne Wren: No, I would say, I don't know if you've looked on the website but there's a new section about driving and when and where you inform people and if you have to for the DVLA. I'm sure Kate will elaborate on that, just to explain the website's got DVLA driving information.

Chairperson (Professor Graham Hughes): Can you grab a microphone, Kate, thanks?

Kate: No, they didn't get back to us at all, so we'll wait. We can do a breakdown on individual kind of conditions such as TIA, strokes or heart attack, it's all on our website, I can't remember, but they never actually got back to us.

Chairperson (Professor Graham Hughes): It's a very, very grey area actually as well, because seizures or petit mal, all forms of epilepsy are seen in our patients early on, in fact there's a study from Italy which looked at teenage epilepsy and found that one in five were positive for antiphospholipid antibodies, which again improves the minute you treat the patients, but of course this affects hugely the risks for getting your license taken away if it's not picked up. I think there's one at the back and then a gentleman at the front.

Q9: Hi, I'm John Allinson. I'm very much in favour of self testing, I've been self testing for a couple of years now. My INR compared to the lab test, the last time it was spot on and it's never more than 0.5, 0.6 out but I think that depends on who you are and what your circumstances are.

In terms of expense, obviously as we've heard, a very good way to fund the cost of the machine is bingo, but to fund the test strips if you have to do that, I wrote on the forum recently that is it cheap and is it expensive, and this is not a comment on individual finance and whether you can afford it or not, but each test is about £270 when you work it out. Now, is that too much to pay? It is a lot, it can be a lot, is it too much to pay for what it might avoid you getting in terms of the dangers of Hughes Syndrome? Just something to consider.

Finally, it's a different question and it's about whether or not Hughes Syndrome is inherited. I know this came up last year and the answer was we don't know, but just before my father died he was complaining of brain fog which is a very common complaint, and I just wondered whether to get my kids tested or not, what would you say about that?

Chairperson (Professor Graham Hughes): I would, I really would, especially obviously important for a girl of 13 or 14 who, the pregnancy issue will be coming up in the future. There is definitely a genetic tendency, as there is to lupus, as there is to all autoimmune diseases; we often see sisters or brothers with thyroid disease, we often see sisters or brothers with MS. So the family of autoimmune diseases have a slight but definite genetic tendency. So if your teenager is getting migraine or is having memory problems or is vaguely unwell I don't think it's being wrong to get them tested, and that's my personal view.

As far as the costs are concerned, we did a study of that some years ago, I wrote a paper about a lady, she may be here actually, from Preston who had Antiphospholipid Syndrome and she used to queue up at the local clinic for a few hours, have her test done, they wouldn't get back to her until the next morning, in which time she'd had another DVT.

She had seven DVTs in a year. I think the local Sainsbury's, or one of the shops, clubbed together and bought her a machine and she self tested, no more admissions to hospital. The cost of machine, £400, cost of seven admissions to hospital, £75,000.

Over here and then the gentleman here.

Q10: Just from your last comment, both of my daughters have been tested and they were both tested because my mum has it and also I had symptoms but I've been tested and given the all clear as well. Both of my daughters get brain fog, they both get migraines and one's collapsed and been hospitalised, they've had MRIs, and both of them have now been diagnosed with Irlen Syndrome.

Chairperson (Professor Graham Hughes): With what?

Q10: Irlen Syndrome

Chairperson (Professor Graham Hughes): I don't know it.

Q10: It's not a very well known syndrome in this country, it's mainly America, Brazil, Japan, Australia, a lot of third world countries have come across Irlen Syndrome. By wearing the Irlen glasses it completely reduces all of their symptoms. My youngest daughter has had vitamin B2 increased and has stopped having the migraines, but it was very, very predominant with both. I was glad that I had them tested to be given the all clear, that actually there was nothing that they could see in any of the blood tests or their history. So thank you.

Chairperson (Professor Graham Hughes): Yes, I agree.

Kate: I was just going to say, anybody that hasn't asked one yet, if we maybe start with them.

Chairperson (Professor Graham Hughes): Yes, would you do that? Who's next? There's a gentleman with his hand up here.

Q11: Gordon Hopkins from Gillingham in darkest north Dorset. First to your comment about DVLA, I had to surrender my licence, I filled in all the forms, sent them back and it took them eight months but they eventually sent me my licence with a letter saying you are safe to drive, even though I'm physically incapable of it at the moment. So that is a bit of a nonsense. But my question was for Craig, you referred to changes in INR due to short term stress. This is something I'd never heard of but is it a well known fact?

Craig Givens: Well, between me and my wife it is. But it was something that I experienced and I wrote it off, I thought maybe I was drinking too much and I looked at my drinking patterns and thought no. Then I noticed every time I would have a serious temper tantrum my INR would shoot up and then I started talking to some other patients, both sitting around in clinic or at times like this and they said yes, stress does affect. One woman, an elderly woman that I used to meet in the clinic, her husband died out of the blue and her INR shot up, way up, like up to ten or 12, and it was there for about four or five weeks before they could get it down. Well no, they got it down, but before they could stabilise it, and the common consensus and her take on it was that it was because of the stress of the death of her husband. And I've heard, I don't know, this is my personal experience.

Sander Otter: Because when I started, this morning I had a little shaving accident and I started my presentation and it was not bleeding. During the presentation it was bleeding and now it's stopped.

Chairperson (Professor Graham Hughes): I like it, lovely. We'll test your INR later. But I mean in all autoimmune

diseases it's known that stress affects, I mean lupus particularly related to this disease that we've got one lady who had two bereavements in a year and after each one the platelets fell to zero and that's physical. Now, there are some hands up at the back and the gentleman in the front.

Q12: Hi there, yeah. I just wanted to talk a little bit, or ask a question about seronegativity really. Myself, I had clear lupus signs for years and at the age of 47 I finally passed a test for that, but despite my clinical incidence of clots in my legs I've always remained persistently negative for Hughes, but take my aspirin twice a day and have improved quite a bit. And both my children have such severe migraines, one has tested positive for lupus now and I have a very sensible paediatrician who's read all your papers and watched the films and both my children have improved a bit on aspirin twice a day. And one has got a lupus test passed now and she's on Plaquinil, but she's had a TIA and they continue to have such severe migraines that my son can only go to school maybe one or two days a week, I have to teach him at home. And they persistently test seronegative as well, so I'm just wondering how soon these new tests will come about, because I really feel they're very much at risk for being overlooked.

Chairperson (Professor Graham Hughes): I fully agree with you and I think Dr Rahman put it very well in his talk, that we're sure, those of us who see hundreds of patients with this that there are patients where the tests are not helpful and let you down. And to give you one example, I've got a pair of identical twins, both with the full house, thrombocytopenia, miscarriages, TIAs, one positive, one negative. They're identical twins, so they both have antiphospholipid. And I think that these committee decisions about diseases is rubbish, they say you must have tests 12 weeks apart just in case you had a transient virus, I get letters off doctors all the time saying we haven't had the second test yet, so she hasn't got the disease. And they limit your sort of thinking about a disease, so with your children with those sort of symptoms you've got to take that seriously.

Kate: Is there anyone that hasn't asked a question yet that wants to ask before we go round for a second time?

Chairperson (Professor Graham Hughes): I can't see, can you tell me, point to the person?

Kate: Yes sorry, is there anyone that hasn't asked one yet that wants to ask one? Okay.

Q13: I just wanted to say something about self testing and then someone asked about the memory problem, and I did speak last year and you looked rather worried because I still had memory problems. And I think perhaps you caught me a little bit late and some of them have stuck, but I did go to the Sicari ((sp?)) place here for 16 sessions of therapy and I had MRIs before and after and I think the big thing is my anticoagulant nurse who helps me along with my self testing, she actually agreed at last to put the INR up higher between three and four, so I was sort of going 3.5 to four and my memory results were quite phenomenal after it went up. It had gone from rock bottom to, I seemed to be a very highly intelligent person and also now I can remember why! So that sort of sings the praises of getting the INR right as well as the self testing.

Chairperson (Professor Graham Hughes): Good, thank you. While we're waiting for the next speaker, I think I mentioned last year, my lady with an INR of 18, she had Hughes Syndrome and it was memory problems and they were getting worse and finally she was diagnosed and treated and ultimately on warfarin and managed very well with an INR of 3.5. Then one day she was given an antibiotic and didn't realise that it messed up your INR and she came into St Thomas' covered with bruises and we did her INR, it was 18. So we all had heart attacks and she said she'd never felt better in her life. She said, I was so sharp I could have composed a symphony!

Q14: Thank you. I recently had twin cousins born, and they were both diagnosed after about a year with autism, and I started reading up on it and it seems that there is a connection between diet and health of the gut and autism, and in general with autoimmune diseases. Also looking on our forum it seems that quite a few people have gluten problems. Are you aware of any research in this field, are you aware of any, I don't know, anything that can be done or



that has to do with diet.

Chairperson (Professor Graham Hughes): Yes, I am, very much so, it's an interest of ours. Yes, you will hear on the grapevine about people whose children have autism, and yes, it has been suggested that there have been patients with both lupus and antiphospholipid who have had offspring with autism. Figures are not known yet and whether that's a real thing or whether it's just the background incidence. Unfortunately some research was blacked, or whatever the phrase is, because it was Andrew Wareham? I've forgotten his name, but published data that - Wakefield - was discredited apparently, he suggested that there was a link between inflammatory bowel disease and autism and that was disproved.

Having said that, there is now interesting data which is coming through, particularly from a group under the leadership of Schoenfeld showing that yes, there are outside influences that do mess up your immune system. For instance, things called adjuvants. Now, aluminium is an adjuvant, it kicks up the immune response, and aluminium is present in all vaccinations and immunisations. And there are these stories of the Gulf War Syndrome who have had multiple immunisations who've developed autoimmune features. So there is a background of interest in this but it's not yet clear, black and white, whether there's a link. I hope that's not too muddy an answer.

Q15: Hi, my name's Claire. I'm just wondering if the foundation, professors, doctors, will they be getting together and trying to lobby Parliament to find out when prescriptions will be free for people with lupus and with antiphospholipid? Because at the end of the day these drugs save our life, why should we have to pay for them so we can live?

Chairperson (Professor Graham Hughes): Would you like to take that, and then Kate at the back?

Beverley Hunt: Yes, our charity is actually part of the coalition against prescription charges. We have lobbies, the government ignores us, they've frozen the pre-payment one you can get, that's the only concession they'll make at the moment, so we are part of a lobbying group already.

Q15: ((inaudible))

Chairperson (Professor Graham Hughes): Sorry, I can't hear you.

Q15: Should the GPs and professors get involved as well? The doctors?

Chairperson (Professor Graham Hughes): ((inaudible))

Q15: Yes, but at the end of the day they're the ones prescribing the drugs, if they know they're saving our lives surely they should help us get free prescriptions?

Chairperson (Professor Graham Hughes): We certainly do, we spend all our spare time lobbying. For instance, recently the government put in a big amount of money towards stroke education and prevention and if you realise that one in five strokes under the age of 45 are aPL positive, so we lobbied them and got no help at all back. And this is very frustrating, but we're trying.

Male speaker: And I'm afraid you're going to have to move to Wales where it's free prescriptions. And being a Welshman I think it's unfair, and in Scotland I think it's actually free as well. But in England, unfortunately where the decisions made by MPs from other parts of the country, like Wales and Scotland and Northern Ireland, I think it's up to us to lobby our own MPs. I have another health problem which is potentially life threatening, but I didn't get free prescriptions either.

Chairperson (Professor Graham Hughes): *I thought all our rules were made in Brussels! One question over here and then the gentleman at the front?*

Q16: *This is in terms of insurance. I was just thinking about your presentation and is it simply the case that someone like myself walks into your office with this lifelong condition of APS that my life insurance, if I took out a life insurance now, my premium would be higher than a normal person walking into your office? In terms of insurance would it be a simple case of, if you're willing to insure, number one, and if yes, would it mean that I would sort of by default have a higher premium than a normal person walking into your office? Because you see, on the contrary I'd like to sort of argue with my insurer that since I have a known condition, since I am being treated by professionals my risk of any eventuality, clinical manifestation, is actually much lower statistically than a person who has not been screened and goes in for life insurance.*

Ed Froggatt: *Yes, funnily enough people that are borderline diabetic, compared to people that are actually diabetic and taking insulin, the insulin dependent diabetic is seen as less of a risk than the person that isn't taking the insulin, so you do have a point there in terms of the risk. In terms of application for life insurance each case would be looked at individually, but I should think that having gone through some type of underwriting the likelihood is that you would receive what is known as a rating where your premium is increased for the cover you're looking for, or the cover that you're looking for is reduced for the premium you're prepared to pay. The level of that rating, so the increased level of premium or reduction in cover would be purely dependent on your health on a case by case basis.*

Edward Beaber: *There's one other thing and that is the report that the doctor, your doctor, provides the insurance company and that –*

Q16: *((inaudible))*

Edward Beaber: *Yes, it would probably be rated.*

Ed Froggatt: *Does that answer the question?*

Q16: *((inaudible))*

Ed Froggatt: *Yes, I mean I think each underwriter and each insurance company would see it differently, which is why we would encourage probably a multi application to certain companies we know to assess how they see the risk of you as an individual for taking out life cover.*

Chairperson (Professor Graham Hughes): *We're getting towards teatime now. Any very burning questions?*

Craig Givens: *Yes. Sorry, I just had one question on the insurance thing. I was intrigued when you talked about the way conditions are responded to by a computer and that if certain things are listed our complications are not actually understood, they're just automatically followed down the line and your advice that it was essential to search out the person in the organisation who actually knew and had knowledge of the condition or the situation. What would your advice be, assuming of course it's going to be to ask your company, but just generally how would you go about searching out that source of information specifically?*

Ed Froggatt: *We would go directly to a senior underwriter at an insurer that we know is likely to offer terms for this type of condition. So when I explained in my part of the presentation about a pre-submission we would effectively run through with a underwriter your specific circumstances, the number of events you've had in the last number of years and they would likely encourage an application or give us a pre underwriting so that's prior to a completed application, an idea of the type of terms they're prepared to offer you, if at all.*

Chairperson (Professor Graham Hughes): *Well, it's teatime and I'm very happy to answer questions personally at tea, but I'd like to thank all the speakers for an absolutely fantastic meeting, thank Kate and her team for arranging it. Thank you.*

